

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
6 December 2001 (06.12.2001)

PCT

(10) International Publication Number
WO 01/92239 A1(51) International Patent Classification⁷: **C07D 263/58, 277/68, 235/26, 413/12, 417/12, A61K 31/423, 31/428, 31/4184, A61P 25/16**

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(21) International Application Number: **PCT/US01/14763**(74) Agents: **FEDERMAN, Evan, J. et al.**; Warner-Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US).(22) International Filing Date: **8 May 2001 (08.05.2001)**(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.(25) Filing Language: **English**(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).(26) Publication Language: **English****Published:**

— with international search report

(30) Priority Data:
60/208,241 31 May 2000 (31.05.2000) US

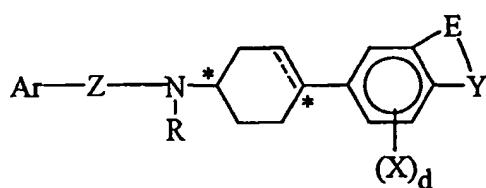
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: BICICLIC CYCLOHEXYLAMINES AND THEIR USE AS NMDA RECEPTOR ANTAGONISTS



specification.

(I)

(57) Abstract: Described are bicycle-substituted cyclohexylamines of Formula (I) and their pharmaceutically acceptable salts thereof. The compounds are antagonists of NMDA receptor channel complexes useful for treating cerebral vascular disorders such as, for example, cerebral ischemia, cardiac arrest, stroke, and Parkinson's disease. The substituents are defined in the

BICYCLIC CYCLOHEXYLAMINES AND THEIR USE AS NMDA RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

The invention pertains to bicycle-substituted cyclohexylamine derivatives
5 as N-Methyl-D-Aspartate Antagonists (NMDA).

BACKGROUND OF THE INVENTION

Over excitation of NMDA receptor channel complexes on postsynaptic neurons following excessive release of glutamic acid from synaptosomes and glutamic acid from synaptosomes and glial cells results in excessive calcium ion 10 influx into the neuronal cells, which leads to their death. This is believed to occur under ischemic or hypoxic conditions such as stroke, hypoglycemic, cardiac arrest and physical trauma. An NMDA receptor antagonist might be therapeutically useful because it may minimize damage of the central nervous system induced by ischemic or hypoxic conditions. The NMDA receptor channel complex consists of at least 15 three binding domains including a glutamic acid (or NMDA) recognition site, a channel blocking binding site, and a strychnine-insensitive glycine binding type. Physiologically, a blockade of at least one of these sites terminates the channel opening of the NMDA receptor to prevent a calcium ion influx. (Nagata R., et al., *J. Med. Chem.*, 1994;37:3956-3968)

20 Excessive excitation of NMDA receptor channel complexes by neurotransmitters may be responsible for the loss of neurons in cerebral vascular disorders such as cerebral ischemia or cerebral infarction resulting in a range of conditions such as thromboembolic or hemorrhagic stroke, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia, such 25 as from near drowning, pulmonary surgery and cerebral trauma, as well as lathyrism, Alzheimer's disease, and Huntington's disease. Such conditions likewise suggest the use of agents that may act as antagonists in the receptors identified above may lead to treatment of amyotrophic lateral sclerosis (ALS),

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schizophrenia, Parkinsonism, epilepsy, anxiety, pain, and drug addiction.

(PCT/EPO 94/01492 having publication number WO 94/26747 published

November 24, 1994, Watjen et al.)

5 L-glutamic acid, L-aspartic acid, and a number of other closely related amino acids have the ability to activate neurons in the nervous system, and therefore the vast majority of excitatory neurons in the mammalian CNS.

Interaction with glutamic acid mediated neurotransmission is considered a useful approach in the treatment of neurological and psychiatric diseases.

(WO 94/26746, published November 24, 1994, Jacobsen et al.)

10 Excitatory amino acid receptor antagonists that block NMDA receptors are recognized for usefulness in the treatment of a variety of disorders. NMDA receptors are intimately involved in the phenomenon of excitotoxicity, which may be a critical determinant of outcome of several neurological disorders.

15 Disorders known to be responsive to blockade of the NMDA receptor include acute cerebral ischemia (stroke or cerebral trauma, for example), muscular spasm, convulsive disorders, neuropathic pain, and anxiety, and may be a significant causal factor in chronic neurodegenerative disorders such as Parkinson's disease (Klockgether T., Turski L., *Ann. Neurol.*, 1993;34:585-59), human immunodeficiency virus (HIV) related neuronal injury, amyotrophic lateral

20 sclerosis (ALS), Alzheimer's disease (Francis P.T., Sims N.R., Procter A.W., Bowen D.M., *J. Neurochem.*, 1993;60(5):1589-1604), and Huntington's disease (see Lipton S., *TINS*, 1993;16(12):527-532; Lipton S.A., Rosenberg P.A., *New Eng. J. Med.*, 1994;330(9):613-622; and Bigge C.F., *Biochem. Pharmacol.*,

25 1993;45:1547-1561 and references cited therein). NMDA receptor antagonists may also be used to prevent tolerance to opiate analgesia or to help control withdrawal symptoms from addictive drugs (European Patent Application 488,959A).

Many of the properties of native NMDA receptors are seen in recombinant homomeric NR1 receptors. These properties are altered by the NR2 subunits.

30 Recombinant NMDA receptors expressed in Xenopus Oocytes have been studied by voltage-clamp recording, and have been found to exhibit developmental and regional expression of the mRNAs encoding NMDA receptor subunits.

Electrophysiological assays were utilized to characterize the actions of

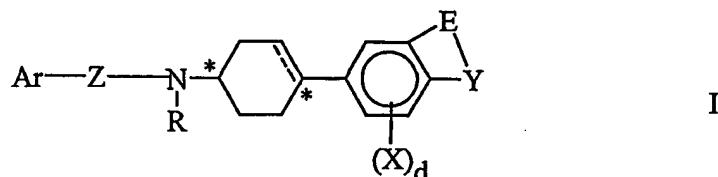
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compounds at NMDA receptors expressed in Xenopus Oocytes. The compounds were assayed at four subunit combinations at cloned rat NMDA receptors, corresponding to three putative NMDA receptor subtypes (Moriyoshi et al., *Nature*, 1991;354:31-37; Monyer et al., *Science*, 1992;256:1217-1221; Kutsuwada et al., *Nature*, 1992;358:36-41; Sugihara et al., *Biochem. Biophys. Res. Commun.*, 1992;185:826-832).

Expression cloning of the first NMDA receptor subunit, NMDAR1 (NR1) in Nakanishi's lab in 1991 provided an initial view of the molecular structure of the NMDA receptor (Moriyoshi et al., *supra*, 1991). There are several other structurally related subunits (NMDAR2A through NMDAR2D) that join NR1 in heteromeric assemblies to form the functional ion channel complex of the receptor (*Annu. Rev. Neurosci.*, 1994;17:31-108). The molecular heterogeneity of NMDA receptors implies a future potential for agents with subtype selective pharmacology.

15 SUMMARY OF THE INVENTION

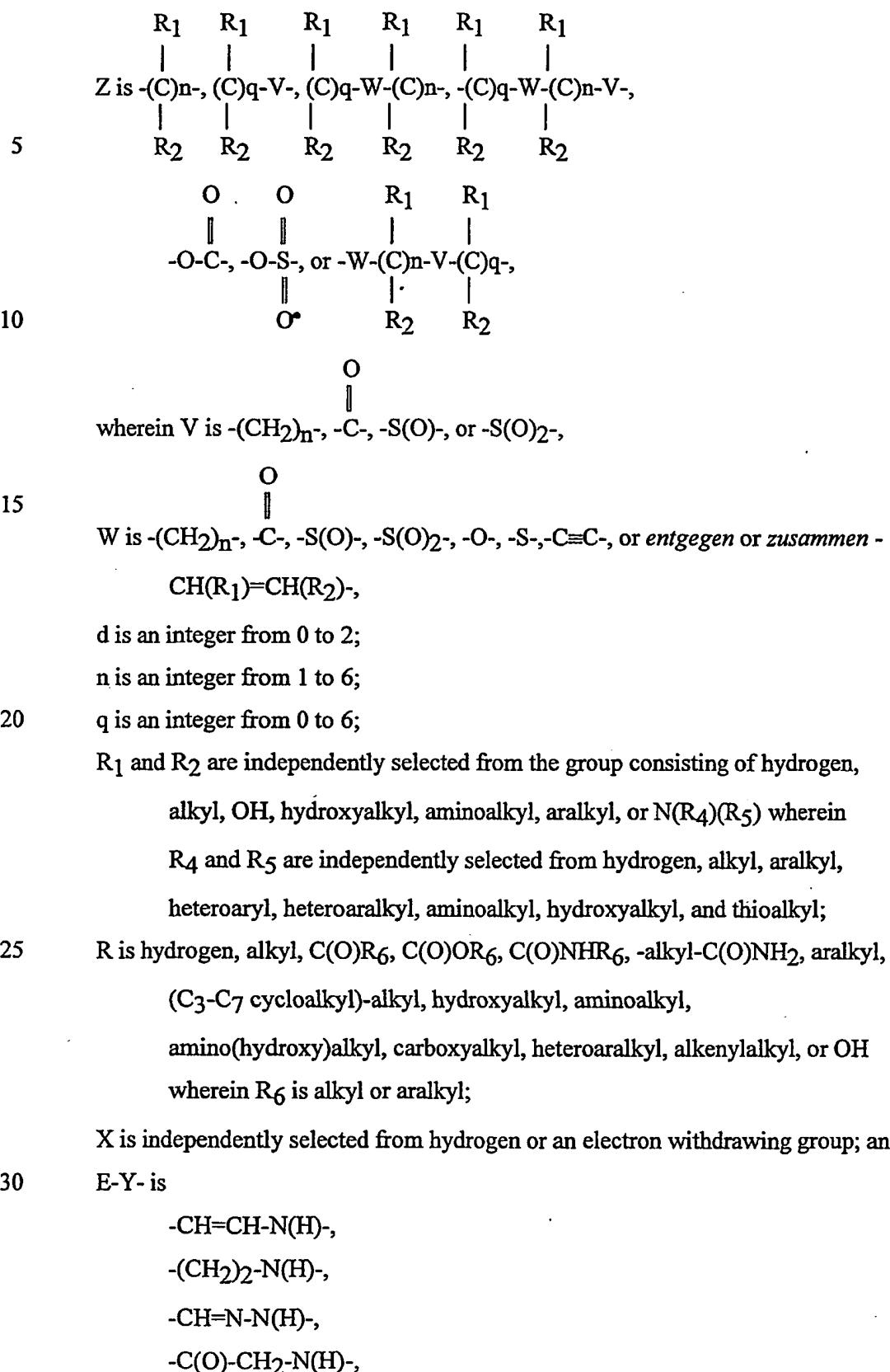
Described are bicycle-substituted cyclohexyl amines of Formula I and their pharmaceutically acceptable salts thereof



wherein:

20 Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to 3 times or
unsubstituted heteroaryl, which heteroaryl is from 5 to 14 atoms having
from 1 to 2 heteroatoms selected from N, O, and S wherein the
substituents are selected from the groups F, Cl, Br, I, OH, NH₂, SH, CN,
NO₂, OCH₃, OC(O)CH₃, CF₃, OCH₂CH₂OH, NHC(O)CH₃, NHCH₃, or
25 N(CH₃)₂;

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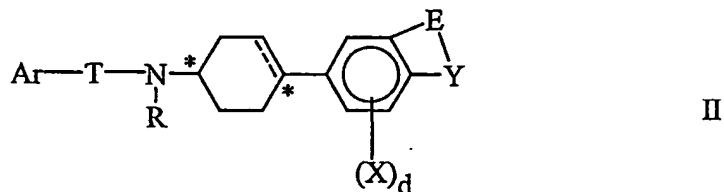
- CH₂-C(O)-N(H)-,
- CH₂-S(O)-N(H)-,
- CH₂-S(O)₂-N(H)-,
- CH=CH-CH(OH)-,
- 5 -(CH₂)₂-CH(OH)-,
- C(O)-CH₂-C(O)-,
- C(O)-NH-C(O)-,
- N=CH-N(H)-,
- N(H)-C(O)-N(H)-,
- 10 -O-C(O)-NH-,
- S-C(O)-NH-,
- O-N=CH(OH)-,
- S-N=CH(OH)-,
- N=N-N(H)-,
- 15 -CH=CH-CH=C(OH)-,
- (CH₂)₃-CH(OH)-,
- (CH₂)₂-S(O)-N(H)-,
- (CH₂)₂-S(O)₂-N(H)-,
- CH=CH-C(O)-N(H)-,
- 20 -C(O)-NH-N=C(OH)-,
- CH=N-NH-C(O),
- CH=N(O)-N=C(OH)-,
- N(H)-C(O)-N(H)-C(O)-,
- N=CH-C(O)-NH-,
- 25 -O-CH₂-C(O)-NH-,
- S-CH₂-C(O)-NH-, or
- N(H)-C(O)-C(O)-N(H)-;

--- denotes a single or double bond; and

* denotes *cis* or *trans* or a mixture thereof.

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The invention also relates to compounds of Formula II



or a pharmaceutically acceptable salt thereof

wherein:

5 Ar, R, X, d, and -E-Y- are as defined above;

T is $(A)_{0-1}N-(U)_{0-1}-(C)_t$ or $(A)_{0-1}-N(C)_t-(U)_{0-1}-$,

10 R₃ R₁ R₃ R₁
 | | | |
 R₂ R₂



wherein U is -CH₂-, -C-, -S(O)-, or -S(O)₂-,

15 A O
 | ||
 A is -CH₂-, -C-, -S(O)-, or -S(O)₂-,

t is an integer from 1 to 3,

R₁ and R₂ are independently selected from hydrogen, alkyl, OH, hydroxyalkyl, aminoalkyl, thioalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, guanidinyl, 20 (aminocarbonyl)alkyl-, carboxyalkyl-, (methylthio)-alkyl-, or N(R₄)(R₅), wherein R₄ and R₅ are independently selected from hydrogen, alkyl, aralkyl, heteroaryl, heteroaralkyl, ureidoalkyl, aminoalkyl, hydroxyalkyl, or thioalkyl;

R₃ is hydrogen, alkyl, OH, or aralkyl;

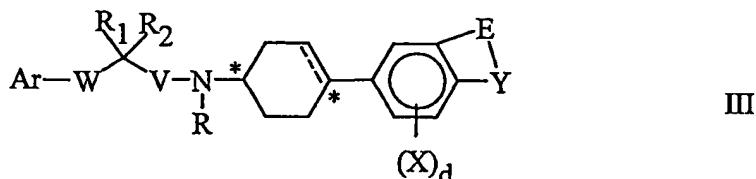
25 R is hydrogen, alkyl, C(O)R₆, C(O)OR₆, C(O)NHR₆, alkyl -CO₂NH₂, aralkyl, hydroxyalkyl, (C₃-C₇ cycloalkyl) alkyl, aminoalkyl, amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenyl-alkyl, or OH wherein R₆ is alkyl or aralkyl;

X is independently selected from hydrogen or an electron withdrawing group; and

30 * denotes *cis* or *trans* or a mixture thereof.

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The invention also relates to compounds of Formula III:



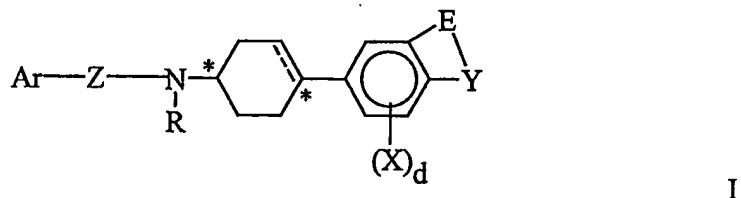
wherein the substituents are defined above.

The invention is also concerned with a pharmaceutical composition useful
5 for treating disorders responsive to the selective blockade of N-methyl-D-
aspartate receptor subtypes utilizing the compounds of Formula I or Formula II or
Formula III and the pharmaceutically acceptable salts thereof, optionally disorders
as stroke, cerebral ischemia, trauma, hypoglycemia, neurodegenerative disorders,
anxiety, depression, migraine headache, convulsions, aminoglycoside antibiotics-
10 induced hearing loss, psychosis, glaucoma, CMV retinitis, opioid tolerance or
withdrawal, chronic pain, or urinary incontinence.

The invention is also concerned with a method of treating disorders responsive to the selective blockade of the N-methyl-D-aspartate receptor subtypes in a mammal suffering thereof which comprises administering in unit dosage form, at least one compound represented by Formula I or Formula II or Formula III above or its pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

The invention is concerned with bicycle-substituted cyclohexylamines of Formula I and their pharmaceutically acceptable salts thereof:



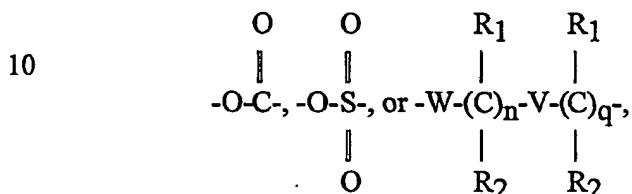
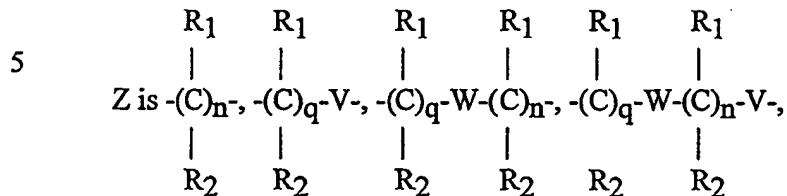
20

wherein:

Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to 3 times or unsubstituted heteroaryl, which heteroaryl is from 5 to 14 atoms having from 1 to 2 heteroatoms selected from N, O, and S wherein the

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substituents are selected from the groups F, Cl, Br, I, OH, NH₂, SH, CN, NO₂, OCH₃, OC(O)CH₃, CF₃, OCH₂CH₂OH, NHC(O)CH₃, NHCH₃, or N(CH₃)₂;



15 O
 |
 wherein V is -(CH₂)_n-, -C-, -S(O)-, or -S(O)₂-,

W is -(CH₂)_n-, -C-, -S(O)-, -S(O)₂-, -O-, -S-, -C≡C-, or *entgegen* or *zusammen*
 20 -CH(R₁)=CH(R₂),

d is an integer from 0 to 2;

n is an integer from 1 to 6;

q is an integer from 0 to 6;

R₁ and R₂ are independently selected from the group consisting of hydrogen,
 25 alkyl, OH, hydroxyalkyl, aminoalkyl, aralkyl, or N(R₄)(R₅) wherein
 R₄ and R₅ are independently selected from hydrogen, alkyl, aralkyl,
 heteroaryl, heteroaralkyl, aminoalkyl, hydroxyalkyl, and thioalkyl;

R is hydrogen, alkyl, C(O)R₆, C(O)OR₆, C(O)NHR₆, -alkyl-C(O)NH₂, aralkyl,
 (C₃-C₇ cycloalkyl)-alkyl, hydroxyalkyl, aminoalkyl,
 30 amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenylalkyl, or OH
 wherein R₆ is alkyl or aralkyl;

X is independently selected from hydrogen or an electron withdrawing group; and
 -E-Y- is

-CH=CH-N(H)-,

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- $(\text{CH}_2)_2\text{-N(H)}$ -,
- $\text{CH}=\text{N-N(H)}$ -,
- $\text{C(O)-CH}_2\text{-N(H)}$ -,
- $\text{CH}_2\text{-C(O)-N(H)}$ -,
- 5 - $\text{CH}_2\text{-S(O)-N(H)}$ -,
- $\text{CH}_2\text{-S(O)}_2\text{-N(H)}$ -,
- $\text{CH}=\text{CH-CH(OH)}$ -,
- $(\text{CH}_2)_2\text{-CH(OH)}$ -,
- $\text{C(O)-CH}_2\text{-C(O)}$ -,
- 10 - C(O)-NH-C(O) -,
- N=CH-N(H) -,
- N(H)-C(O)-N(H) -,
- O-C(O)-NH -,
- S-C(O)-NH -,
- 15 - O-N=CH(OH) -,
- S-N=CH(OH) -,
- N=N-N(H) -,
- $\text{CH}=\text{CH-CH=C(OH)}$ -,
- $(\text{CH}_2)_3\text{-CH(OH)}$ -,
- 20 - $(\text{CH}_2)_2\text{-S(O)-N(H)}$ -,
- $(\text{CH}_2)_2\text{-S(O)}_2\text{-N(H)}$ -,
- $\text{CH}=\text{CH-C(O)-N(H)}$ -,
- C(O)-NH-N=C(OH) -,
- $\text{CH}=\text{N-NH-C(O)}$ -,
- 25 - $\text{CH}=\text{N(O)-N=C(OH)}$ -,
- $\text{N(H)-C(O)-N(H)-C(O)}$ -,
- N=CH-C(O)-NH -,
- $\text{O-CH}_2\text{-C(O)-NH}$ -,
- $\text{S-CH}_2\text{-C(O)-NH}$ -, or
- 30 - $\text{N(H)-C(O)-C(O)-N(H)}$;- and

* denotes *cis* or *trans* or a mixture thereof.

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In the compounds of the present invention preferred are compounds of Formula I or pharmaceutically acceptable salts thereof wherein:

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF₃, C(O)CH₃, and haloalkyl.

More preferred are compounds of Formula I or pharmaceutically acceptable salts thereof wherein:

Ar is unsubstituted or substituted phenyl;

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF₃, C(O)CH₃, and haloalkyl; and

$$\begin{array}{c} \text{O} & \text{O} \\ || & || \\ -\text{E}-\text{Y}- \end{array}$$
 is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-;

$$\begin{array}{c} \text{O} & \text{O} \text{ O} \\ || & || \\ -\text{NH}-\text{C}-\text{NH}, -\text{N}=\text{N}-\text{NH}, \text{ and } -\text{NH}-\text{C}-\text{C}-\text{NH}-; \end{array}$$

* denotes *trans*.

Still more preferred are compounds of Formula I or pharmaceutically acceptable salts thereof wherein:

Ar is unsubstituted or substituted phenyl;

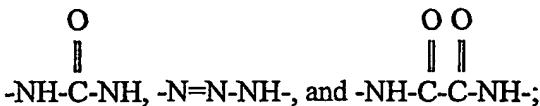
R is hydrogen, methyl, heteroaralkyl, (C₃-C₇ cycloalkyl)alkyl, alkenylalkyl, H₂NC(O)alkyl, or C(O)CH₃;

$$\begin{array}{c} \text{O} & \text{CH}_3 \\ || & || \\ \text{Z} \text{ is } -\text{CH}_2-(\text{CH}_2)_m-, -(\text{CH}_2)_m-\text{C}-, -\text{O}-(\text{CH}_2)_m-, -(\text{CH}_2)_m-\text{CH}-, \\ -(\text{CH}_2)_m-\text{CH}-\text{CH}_2-, -\text{O}-\text{C}-\text{C}-, -\text{S}-(\text{CH}_2)_m-, -\text{C}\equiv\text{C}-\text{CH}_2, \text{ or } -\text{C}\equiv\text{C}-(\text{CH}_2)_2- \end{array}$$

wherein m is an integer 2 or 3;

$$\begin{array}{c} \text{O} & \text{O} \\ || & || \\ -\text{E}-\text{Y}- \end{array}$$
 is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-;

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X is hydrogen; and

5 * denotes *trans*.

Most preferred are compounds of Formula I selected from those listed below:

- 6-[*trans*-4-(3-Phenylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[2-(4-Fluorophenoxy)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 10 6-[*trans*-4-(2-Phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 15 6-{*cis*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-[*trans*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-[*cis*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 20 6-[4-(3-Phenylpropylamino)cyclohex-1-enyl]-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[2-(4-Fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 25 6-{*trans*-4-[(*R*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[(*S*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 30 6-{*trans*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*cis*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 30 6-{*trans*-4-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-[*cis*-4-(3-p-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-[*trans*-4-(3-p-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

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6-[*trans*-4-(2-Benzenesulfinylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
6-[*trans*-4-(2-Benzenesulfonylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
5 6-{*trans*-4-[Methyl(3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
10 6-(*cis*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
6-{*trans*-[4-(2-Methyl-3-phenylpropylamino)cyclohexyl]}-3*H*-benzoxazol-2-one;
15 6-{*trans*-4-[Methyl(2-methyl-3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
6-{*trans*-[4-(3-Phenyl-prop-2-ynylamino)cyclohexyl]}-3*H*-benzoxazol-2-one;
20 6-{*trans*-4-[Methyl(3-phenylprop-2-ynyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
6-{*trans*-4-[2-(4-Fluorophenylsulfanylethyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
25 6-{*trans*-4-[3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
6-{*trans*-4-[Methyl-3-(p-tolylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
30 6-{*trans*-4-[Methyl(2-phenoxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
6-{*trans*-4-[Methyl-3-(4-trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
6-{*trans*-4-[3-(2,4-Difluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
6-(*trans*-4-{[3-(2,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

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6-(*trans*-4-{[3-(4-Isopropylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Isobutylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

5 6-(*trans*-4-{[Ethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{Ethyl-[3-(4-trifluoromethylphenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

10 6-(*trans*-4-{Ethyl-[*(R*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{Ethyl-[*(S*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-{*trans*-4-[[3-(4-Fluorophenyl)propyl]-2-hydroxyethyl]amino}-cyclohexyl}-3*H*-benzoxazol-2-one;

15 6-(*trans*-4-{Cyclopropylmethyl-[3-(4-fluorophenyl)propyl]-amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]furan-3-ylmethylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;

20 6-(*trans*-4-{Allyl-[3-(4-Fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]isobutylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{(2-Aminoethyl)-[3-(4-fluorophenyl)propyl]amino}-cyclohexyl)-3*H*-benzoxazol-2-one;

25 2-{[3-(4-Fluorophenyl)propyl]-[4-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-cyclohexyl]amino}acetamide;

(S)-6-{*trans*-4-[1-(4-Fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

30 (S)-6-{*trans*-4-[Ethyl(1-(4-fluorophenylsulfanyl)pentan-2-yl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-[*trans*-4-(3-Phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

6-[*trans*-4-(Methyl-3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

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6-{*trans*-4-[3-(4-Chlorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Chlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

5 6-(*trans*-4-{[3-(2,4-Dichlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-[3-(3,5-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;

10 6-(*trans*-4-{[3-(3,5-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-[3-(3,4-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(3,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

15 6-(*trans*-4-{[3-(2,3,4-Trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(4-{[3-(*trans*-4-Dimethylaminophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;

20 6-(*trans*-4-{[3-(2,4,6-Trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-4-[3-(2,4-Dimethylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;

6-(*trans*-{4-[Methyl(2,4-dimethylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one;

25 6-{*trans*-4-[3-(2-Chloro-4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(2-Chloro-4-fluorophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;

30 6-{*trans*-4-[3-(4-Chloro-2-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

6-(*trans*-4-{[3-(4-Chloro-2-fluorophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;

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- 6-(*trans*-4-[3-(4-Fluoro-2-methylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-{4-[Methyl(4-fluoro-2-methylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one;
- 5 6-{*trans*-4-[3-(3-Fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(3-Fluoro-2-methylphenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;
- 10 6-{*trans*-4-[3-(2-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(2-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 15 6-{*trans*-4-[3-(3-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(3-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 20 6-{*trans*-4-[{(3-Cyclohexylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[{(3-Cyclohexylpropyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 25 6-{*trans*-4-[4-(3-Thiophen-3-yl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-[*trans*-4-{[3-(3-Thiophen-3-yl)propyl]methylamino}cyclohexyl]-3*H*-benzoxazol-2-one;
- 30 6-{*trans*-4-[Methyl(3-thiazol-2-ylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{Methyl-[2-(methylphenylamino)ethyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;
- N-(2-{Methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-ethyl)benzamide;
- N-{2-[4-(2-Oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexylamino]-ethyl}benzamide;

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6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzthiazol-2-one;

3-(4-Fluorophenyl)-N-methyl-N-[*trans*-4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]propionamide;

5 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzthiazol-2-one;

5-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-1,3-dihydrobenzoimidazol-2-one;

10 5-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-1,3-dihydrobenzoimidazol-2-one;

6-(4-{[3-(4-Fluorophenyl)propyl]methyl-amino}cyclohexyl)-5-methyl-3*H*-benzoxazol-2-one; and

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-5-methoxy-3*H*-benzoxazol-2-one.

15 Preferred are compounds of Formula II or pharmaceutically acceptable salts thereof wherein:

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF₃, C(O)CH₃, and haloalkyl.

20 More preferred are compounds of Formula II or pharmaceutically acceptable salts thereof wherein:

Ar is unsubstituted or substituted phenyl;

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF₃, C(O)CH₃, and haloalkyl; and



-E-Y- is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-;



-NH-C-NH, -N=N-NH-, and -NH-C-C-NH-; and

* denotes *trans*.

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Still more preferred are compounds of Formula II or pharmaceutically acceptable salts thereof wherein:

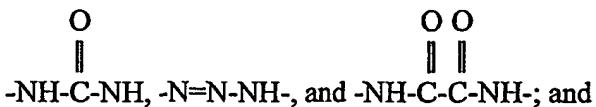
Ar is unsubstituted or substituted phenyl;

Ar and the nitrogen atom bearing R are separated by 3 or 4 atoms;

- 5 X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, CF₃, C(O)CH₃, and haloalkyl;



10 -E-Y- is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-;

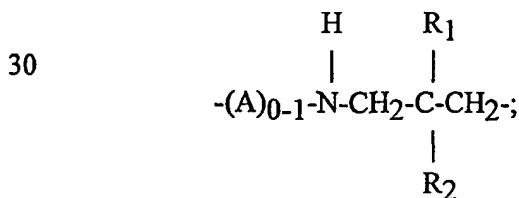
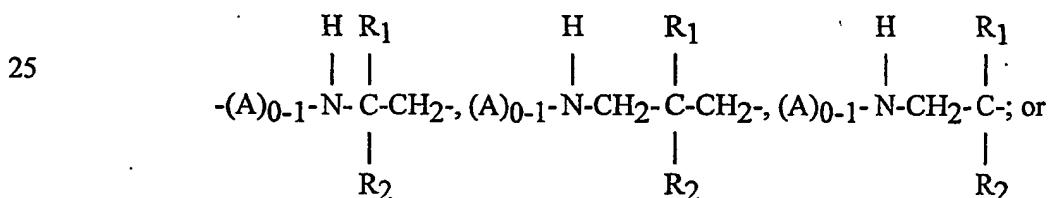
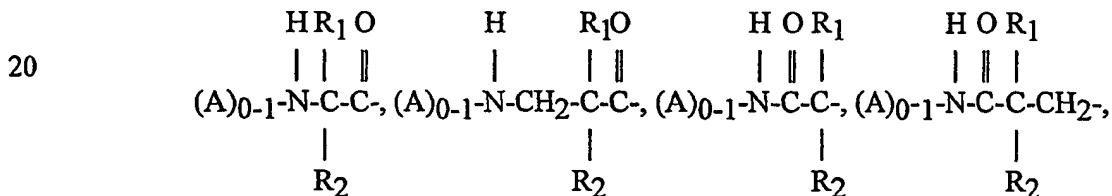


* denotes *trans*.

- 15 Still more preferred are compounds of Formula II or pharmaceutically acceptable salts thereof wherein:

Ar is unsubstituted or substituted phenyl;

T is



R is hydrogen or methyl or heteroaralkyl or (C₃-C₇ cycloalkyl) alkyl;

35 H₂NC(O)alkyl, alkenylalkyl, or C(O)CH₃;

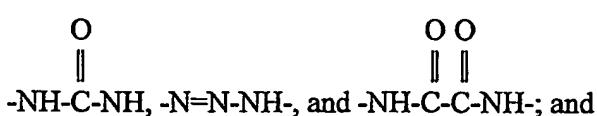
X is hydrogen; and

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-E-Y- is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-;

5



* denotes *trans*.

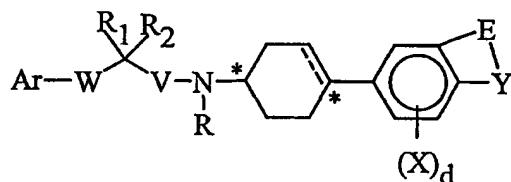
Preferred compounds of Formula II are:

6-[*trans*-4-(2-Phenylaminoethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

10 and

N-(2-{Methyl[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-ethyl)benzamide.

Another preferred compound is that of Formula III



III

15 with the substituents as described above for Formula I.

Other preferred compounds of Formula III are:

Ar is unsubstituted or substituted phenyl;

X is independently selected from hydrogen or an electron withdrawing group

selected from the group consisting of halogen, nitro, cyano, aminoalkyl,

20 CF₃, C(O)CH₃, and haloalkyl; and



-E-Y- is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-;

25



-NH-C-NH, -N=N-NH-, and -NH-C-C-NH-; and

* denotes *cis* or *trans*.

Other preferred compounds are compounds of Formula I, Formula II, or

Formula III wherein:

30



-E-Y- is -O-C-NH-.

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Other preferred compounds are compounds of Formula I, Formula II, or Formula III wherein:



5 -E-Y- is -NH-C(=O)-NH-.

Other preferred compounds are compounds of Formula I, Formula II, or Formula III wherein:



10 -E-Y- is -SC(=O)-NH-.

Preferably the pharmaceutical compositions are useful for the treatment of the neurodegenerative disorder Parkinson's disease.

Preferably, the pharmaceutical compositions are useful as a dopamine agonist or precursor thereof in amount effective to treat Parkinson's disease.

15 Other preferred compounds are those where * denotes *cis*.

The diradical group E-Y must contain a hydrogen bond donor functionality.

The term "alkyl" means a straight or branched hydrocarbon radical having from 1 to 12 carbon atoms unless otherwise specified, also known as a C₁-C₁₂

20 alkyl, and includes, for example, methyl, ethyl, 1-propyl, and 2-propyl, 1-butyl, 2-butyl, 2-methyl-1-propyl, 1,1-dimethylethyl, 1-pentyl, 2-pentyl, 3-pentyl, 2,2-dimethylpropyl, 1-hexyl, 2-hexyl, 3-hexyl, 4-methyl-1-pentyl, 1-heptyl, 2-heptyl, 3-heptyl, 4-heptyl, 5-methyl-1-hexyl, 1-octyl, 2-octyl, 3-octyl, 4-octyl, 6-methyl-1-heptyl, 5,5-dimethylhexyl, 1-nonyl, 2-nonyl, 1-decyl, 2-decyl, 25 1-undecyl, 2-undecyl, 1-dodecyl, and 5-dodecyl. Alkyl groups may be unsubstituted or independently substituted by from 1 to 3 substituents selected from F, Cl, Br, I, OH, NH₂, SH, CN, NO₂, OCH₃, OC(O)CH₃, CF₃, OCH₂CH₂OH, NHC(O)CH₃, NHCH₃, or N(CH₃)₂.

30 Alkyl groups having two or more carbons may optionally contain 1 or 2 sites of unsaturation, the groups being known as alkenyl groups or radicals.

Illustrative examples of an alkenyl group or radical having from 2 to 12 carbon atoms, also known as a C₂-C₁₂ alkenyl, include ethenyl, 1-propenyl, 2-propenyl, 1-buten-1-yl, 2-buten-1-yl, 1-penten-1-yl, 2-penten-1-yl, 1-penten-3-yl, 1-penten-

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5-yl, 1-hexen-1-yl, 1-hexen-4-yl, 2-hexen-1-yl, 3-hexen-1-yl, 2-octen-3-yl, 5-nonen-2-yl, 4-undecen-4-yl, and 5-dodecen-2-yl.

The term "aryl" means an aromatic carbocyclic ring having from 6 to 10 carbon atoms. Illustrative examples of an aryl group or radical include phenyl, 5 1-naphthyl, and 2-naphthyl. Aryl groups may be unsubstituted or independently substituted by from 1 to 3 substituents selected from F, Cl, Br, I, OH, NH₂, SH, CN, NO₂, OCH₃, OC(O)CH₃, CF₃, OCH₂CH₂OH, NHC(O)CH₃, NHCH₃, or N(CH₃)₂.

The term "aralkyl" means an aryl-alkyl- group or radical wherein aryl and 10 alkyl have the meanings as defined above. Illustrative examples of an arylalkyl group or radical include benzyl, 4-fluorophenylmethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 3-methyl-3-phenylpropyl, 1-naphthylmethyl, 1-naphthylethyl, 3-(1-naphthyl)-propyl, 4-(1-naphthyl)-butyl, 4-(2-naphthyl)-butyl, 4-phenylheptyl, and 12-(2-hydroxyphenyl)-dodec-3-yl.

15 The term "(C₃-C₇ cycloalkyl)-alkyl" means an "alkyl" group (as described above) substituted thereon by a cycloalkyl group of from 3 to 7 carbon atoms such as cyclopentyl, cyclopropyl, cyclohexyl, or cycloheptyl.

The term "heteroatom" means nitrogen, oxygen, or sulfur.

20 The term "heteroaryl" means an unsaturated monocyclic group or radical of 5 or 6 atoms, an unsaturated fused bicyclic group or radical of from 8 to 10 atoms, or an unsaturated fused tricyclic group or radical of from 11 to 14 atoms, the cyclic groups having 1 or 2 heteroatoms independently selected from O, N, or S. Heteroaryl does not contain a hydrogen bond donor diradical group E-Y. Illustrative examples of monocyclic heteroaryl include 2- or 3-thienyl, 25 2- or 3-furanyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, 2-, 4-, or 5-oxazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isoxazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 3-, or 4-pyridinyl, 3- or 4-pyridazinyl, 2- or 3-pyrazinyl, and 2-, 4- or 5-pyrimidinyl. Illustrative examples of bicyclic heteroaryl include 2-, 3-, 4-, 5-, 6-, 7-, or 30 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 1-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5-, 6-, or 7-benzofuran, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl, and 1-benzimidazolyl. Illustrative examples of tricyclic heteroaryl include 1-, 2-, 3-, or 4-dibenzofuranyl, 1-, 2-, 3-, or

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4-dibenzothienyl and 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-(1,2,3,4-tetrahydroacridinyl).

All with the proviso that when Z in Formula I is attached via a heteroatom, Z is attached to a carbon atom of the heteroaryl group or radical. Heteroaryl groups may be unsubstituted or independently substituted by from 1 to 3 substituents selected from F, Cl, Br, I, OH, NH₂, SH, CN, NO₂, OCH₃, OC(O)CH₃, CF₃, OCH₂CH₂OH, NHC(O)CH₃, NHCH₃, or N(CH₃)₂.

As used above, a fused bicyclic group or radical is a group wherein 2 ring systems share two and only 2 atoms.

As used above, a fused tricyclic group or radical is a group wherein 3 ring systems share four and only 4 atoms.

“—” denotes a single or double bond.

The term “heteroaralkyl” means a heteroaryl-alkyl- group or radical wherein heteroaryl and alkyl have the meanings as defined above. Illustrative examples of an heteroaralkyl group or radical include 4-pyridyl-methyl, (4-fluoroquinolin-2-yl)methyl, 2-(isoxazol-3-yl)ethyl, and 12-(5-chlorothiophen-2-yl)-dodec-3-yl.

The term “halogen” means bromine, chlorine, fluorine, or iodine.

The term “aminoalkyl” means an H₂N-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least one substituent is -NH₂.

The term “hydroxyalkyl” means an HO-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is -OH.

The term “amino(hydroxy)alkyl” means an H₂N(HO)-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 2 or 3 substituents wherein at least 1 substituent is OH and 1 substituent is -NH₂.

The term “(aminocarbonyl)alkyl” means an H₂NC(O)-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is -(O)C-NH₂.

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The term "thioalkyl" means an HS-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is -SH.

5 The term "alkenylalkyl" means a (C₂-C₁₂ alkenyl)-(C₁-C₁₂ alkyl) group or radical wherein C₂-C₁₂ alkenyl and C₁-C₁₂ alkyl are as defined above.

The term "(methylthio)-alkyl-" means an CH₃S-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is -SCH₃.

10 The term "carboxyalkyl" means an HO₂C-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least one substituent is -CO₂H.

15 The term "haloalkyl" means a halogen-alkyl- group or radical wherein halogen and alkyl have the meanings as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is selected from F, Cl, Br, or I.

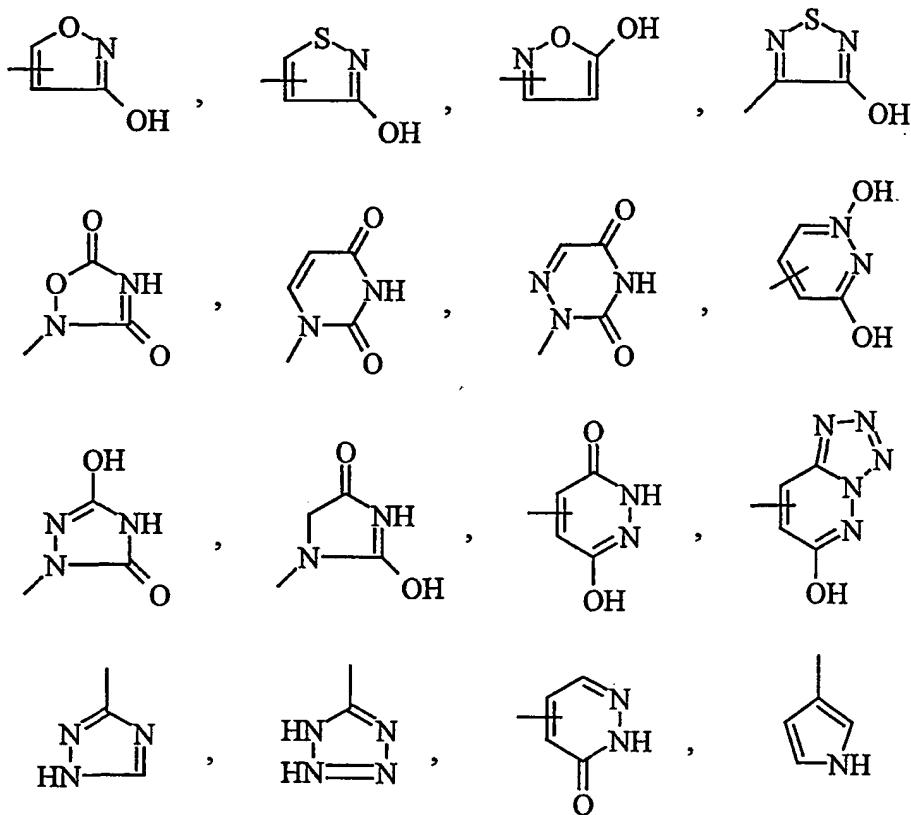
20 The term "ureidoalkyl" means an H₂N-(C=O)-NH-alkyl- group or radical wherein alkyl has the meaning as defined above, which is a substituted alkyl group or radical containing from 1 to 3 substituents wherein at least 1 substituent is H₂N-(C=O)-NH-.

25 The term "electron withdrawing group" means a group or radical selected from halogen, nitro, cyano, alkyl, CF₃, C(O)CH₃, P(O)(O-R₉)₂, SO₂-R₉, SO₂NHR₉, C(O)NR₉R₉' wherein R₉ is independently selected from C₁-C₆ alkyl or unsubstituted or substituted phenyl, -(C=NH)-NH₂, -(C=NH)-O-alkyl, methoxymethyl, or haloalkyl, wherein the substituents may be F, Cl, Br, I, OH, NH₂, SH, CN, NO₂, OCH₃, OC(O)CH₃, CF₃, OCH₂CH₂OH, NHC(O)CH₃, NHCH₃, or N(CH₃)₂.

30 The phrase "heterocycle, which heterocycle is a carboxylic acid or an amide isostere" means a 5- or 6-membered monocyclic ring containing from 1 to 4 heteroatoms selected from N, O, and S and providing a hydrogen bond

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donor moiety selected from NH, OH, and SH. Illustrative examples include the following structures:



5

10

See also Greenwood J.R., Vaccarella G., Cooper H.R., Allan R.D., Johnston G.A.R, *Internet Journal of Chemistry*, 1998;1(38)(Chart 4). Additional examples are well-known to the skilled artisan. (See, for example, (i) Lipinski

C.A., *Annual Reports in Medicinal Chemistry*, 1986;21:Chaps 21, 27; (ii) Thornber C.W., *Chem. Soc. Rev.*, 1979;8:563; (iii) Burger A., *Progress in Drug Research*, 1991;37:288-371.

15

The term "entgegen" means the stereoisomerism about a carbon-carbon double bond wherein the highest ranking substituent on each carbon are on opposite sides, which substituent ranking is based on the sequence rules of the Cahn-Ingold-Prelog system (March J., *Advanced Organic Chemistry*, 4th ed., New York: John Wiley & Sons 1992:109, 127 and references cited therein).

The term "zusammen" means the stereoisomerism about a carbon-carbon double bond wherein the highest ranking substituent on each carbon are on the

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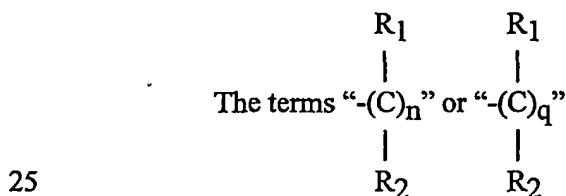
same side, which substituent ranking is based on the sequence rules of the Cahn-
Ingold-Prelog system (March J., *supra.*, 1992).

The term “*cis*” means the stereoisomerism about a carbon-carbon double
bond, a monocyclic ring, a fused bicyclic ring, or a bridged bicyclic ring wherein
5 the highest ranking substituent on each of the two carbons of relevance are on the
same side, which substituent ranking is based on the sequence rules of the Cahn-
Ingold-Prelog system (March J., *supra.*, 1992).

The term “*trans*” means the stereoisomerism about a carbon-carbon double
bond, a monocyclic ring, a fused bicyclic ring, or a bridged bicyclic ring wherein
10 the highest ranking substituent on each of the two carbons of relevance are on
opposite sides, which substituent ranking is based on the sequence rules of the
Cahn-Ingold-Prelog system (March J., *supra.*, 1992).

The terms “*cis*” or “*trans*” refers to the relative stereochemistry of the
groups attached to the cyclohexyl rings of Formulas I or II at the carbon atoms
15 denoted by “*”.

The term “(X)_d” means the group X is present 1 or 2 times on the
phenylene to which it is attached, which group is independently selected from
hydrogen or an electron withdrawing group wherein the electron withdrawing
group is as defined above unless otherwise stated. The groups X can be the same
20 or different.



wherein n is an integer of from 1 to 6 and q is an integer of from 0 to 6 mean a
chain of from 1 to 6 carbons or from 0 to 6 carbons, respectively, wherein each
carbon is independently substituted, which substituents are the groups R₁ and R₂,
wherein R₁ and R₂ are independently (R₁ and R₂ in each occurrence can be the
30 same or different) selected from the groups consisting of hydrogen, alkyl, OH,
hydroxyalkyl, aminalkyl, aralkyl, or N(R₄)(R₅) wherein R₄ and R₅ are
independently selected from hydrogen, alkyl, aralkyl, heteroaryl, heteroaralkyl,

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aminoalkyl, hydroxyalkyl and thioalkyl, unless otherwise stated. The groups R₁ can be the same or different and the groups R₂ can be the same or different.

The group -E-Y-, together with the phenyl to which it is attached, is a bicyclic that contains a hydrogen bond donor functionality.

For purposes of the syntheses of the compounds of the present invention, reactive functional groups present in starting materials, reaction intermediates, or reaction products may be protected during chemical reactions using protecting groups which render the reactive functional groups substantially inert to the reaction conditions (see, for example, Green T., Wuts P.G., *Protective Groups in Organic Synthesis*, 2nd ed., New York: John Wiley & Sons, 1991). Thus, for example, protecting groups such as the following may be utilized to protect suitable amino, hydroxyl, and other groups of related reactivity: carboxylic acyl groups, such as formyl, acetyl, trifluoroacetyl; alkoxy carbonyl groups, such as ethoxycarbonyl, *t*-butoxycarbonyl (BOC), β,β,β -trichloroethoxycarbonyl (TCEC), β -iodoethoxycarbonyl; aryloxycarbonyl groups, such as benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, phenoxy carbonyl; trialkyl silyl groups, such as trimethylsilyl and *t*-butyldimethylsilyl (TBDMS); and groups such as trityl, tetrahydropyranyl, vinyloxycarbonyl, *o*-nitrophenylsulfenyl, diphenylphosphinyl, *p*-toluenesulfonyl, and benzyl may all be utilized. The protecting group may be removed, after completion of the synthetic reaction of interest, by procedures known to those skilled in the art. For example, a BOC group may be removed by acidolysis, a trityl group by hydrogenolysis, TBDMS by treatment with fluoride ions, and TCEC by treatment with zinc

Certain of the compounds of the present invention possess one or more chiral centers and each center may exist in the R or S configuration. The present invention includes all diastereomeric, enantiomeric, and epimeric forms as well as the appropriate mixtures thereof. Additionally, the compounds of the present invention may exist as geometric isomers. The present invention includes all *cis*, *trans*, *syn*, *anti*, entgegen (E), and zusammen (Z) isomers as well as the appropriate mixtures thereof.

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Some of the compounds of Formula I-III are capable of further forming pharmaceutically acceptable acid-addition and/or base salts. All of these forms are within the scope of the present invention.

- Pharmaceutically acceptable acid addition salts of the compounds of
5 Formula I-III include salts derived from nontoxic inorganic acids such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydroiodic, hydrofluoric, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, trifluoroacetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinates suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phthalate, benzenesulfonate, toluenesulfonate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge S.M., et al., *Journal of Pharmaceutical Science*, 1977;66:1-19).
- 20 The acid addition salt of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner.

Pharmaceutically acceptable base addition salts are formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of
25 metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are N,N-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, dicyclohexylamine, ethylenediamine, N-methylglucamine, and procaine (see, for example, Berge, supra., 1977).

The base addition salts of said acidic compounds are prepared by
30 contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated

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forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. Thus, the compounds of the present invention can be administered by injection, that is, intravenously, 5 intramuscularly, intracutaneously, subcutaneously, intraduodenally, or intraperitoneally. Also, the compounds of the present invention can be administered by inhalation, for example, intranasally. Additionally, the compounds of the present invention can be administered transdermally. It will be 10 obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I-III or a corresponding pharmaceutically acceptable salt of a compound of Formula I-III.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or 15 liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with 20 the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from 5% or 10% to about 70% 25 of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a 30 capsule in which the active component with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

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For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted, and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection, liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing, and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or, synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations, which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferably in unit dosage form. In such form the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 0.1 to 100 mg preferably 0.5 to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

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In therapeutic use as antagonists or as agents for the treatment of diseases, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 0.01 to about 100 mg/kg daily. A daily dose range of about 0.01 to about 10 mg/kg is preferred. The dosages, however, 5 may be varied depending upon the requirements of the patient, the severity of the condition being treated, the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages, which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the 10 optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

Tablet Formulation

Ingredient	Amount (mg)
Example 1	25
Lactose	50
Cornstarch (for mix)	10
Cornstarch (for paste)	10
Magnesium stearate (1%)	5
Total	100

Example 1, lactose and cornstarch (for mix) are blended to uniformity. The 15 cornstarch (for paste) is suspended in 200 mL of water and heated with stirring to form a paste. The paste is used to granulate the mixed powders. The wet granules are passed through a No. 8 hand screen and dried at 80°C. The dry granules are lubricated with the 1% magnesium stearate and pressed into a tablet. Such tablets can be administered to a human from one to four times a day for treatment of 20 disease caused by over excitation of NMDA receptor channel complexes.

The compounds of the present invention can be prepared according to the various synthetic schemes that follow. Protecting groups may be used when

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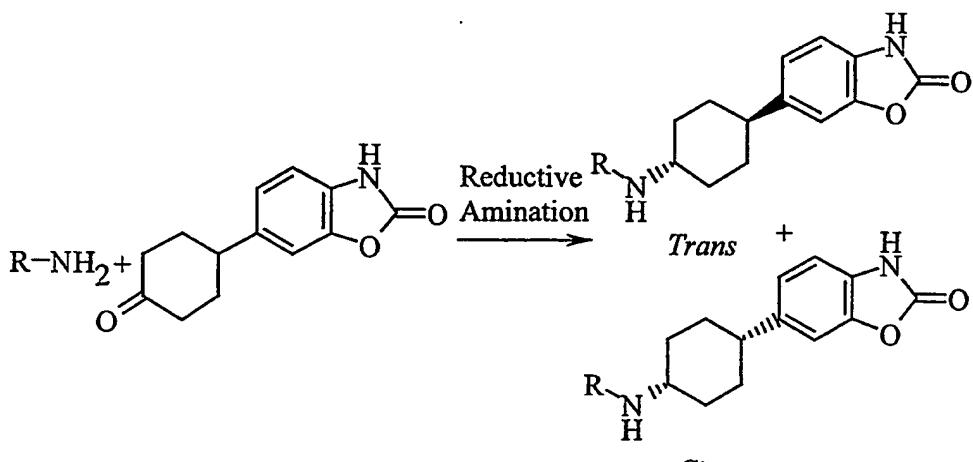
appropriate throughout many of the schemes. Although specifically noted in certain schemes, the appropriate use and choice of protecting groups is well known by one skilled in the art, and is not limited to the specific examples below. It is also understood that such groups not only serve to protect chemically reactive sites, but also to enhance solubility or otherwise change physical properties. A good general reference for protecting group preparation and deprotection is “Protective Groups in Organic Synthesis”(Green T., *supra.*, 1991). A number of general reactions such as oxidations and reductions are not shown in detail but can be done by methods understood by one skilled in the art. General transformations are well-reviewed in “Comprehensive Organic Transformation” by Richard Larock, and the series “Compendium of Organic Synthetic Methods” published by Wiley-Interscience, 1989. In general, the starting materials were obtained from commercial sources unless otherwise indicated.

PREPARATION OF COMPOUNDS

15 Benzoxazolines

In general, these compounds can be prepared by a reductive amination reaction between an amine and 6-(4-cyclohexanonyl)benzoxazolin-2-one **5** (Scheme 1). A synthetic procedure for the synthesis of **5** is shown in Scheme 2.

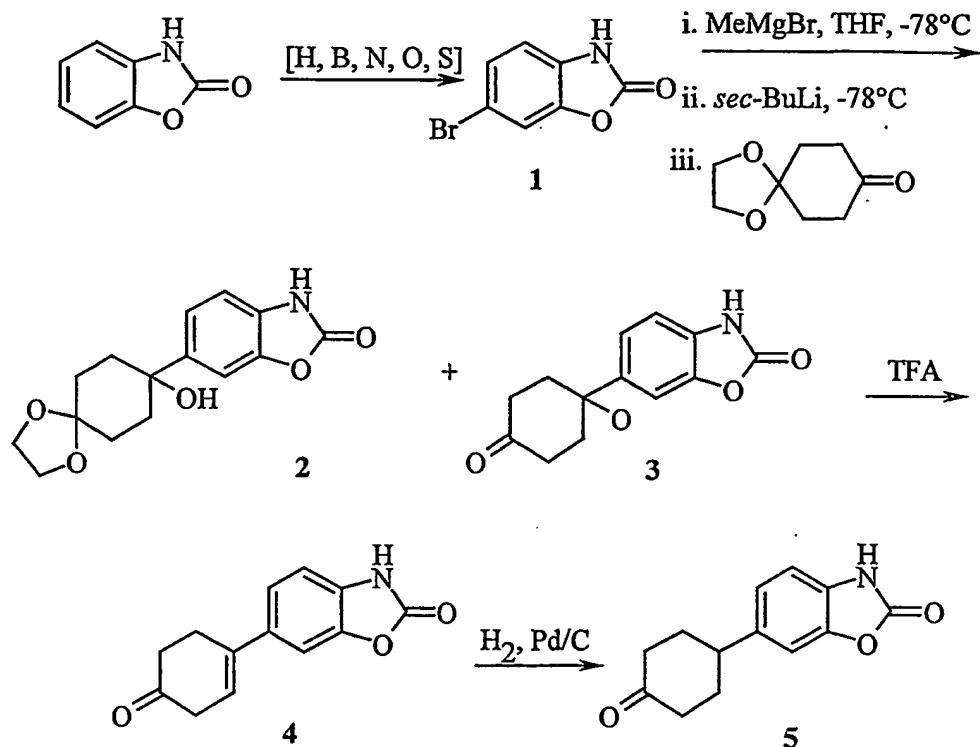
Scheme 1



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Scheme 2

Preparation of 6-(4-Cyclohexanonyl)benzoxazolin-2-one 5



Step 1: *N*-Bromosuccinimide (26.6 g, 0.15 mol) was added to a stirred solution of 2-benzoxazolinone (20.0 g, 0.15 mol) in glacial acetic acid (220 mL), and the mixture was stirred at room temperature for 3 days. The reaction mixture was poured into H₂O (1.2 L), and the white solid that formed was collected. Recrystallization from hot EtOH (300 mL) gave bromide 1 (22.1 g, 70%) as an off-white solid: mp 190-195°C; IR (KBr): 3278, 1779, 1736, 1623 cm⁻¹; ¹H NMR (300 MHz, CD₃OD): δ 7.41 (d, *J* = 2 Hz, 1H), 7.32 (dd, *J* = 5, 2 Hz, 1H), 6.99 (d, *J* = 5 Hz, 1H); CI MS (methane) (*m/z*): 215 [M + H]⁺.

Step 2: Bromide 1 (12.8 g, 59.6 mmol) was dissolved in anhydrous THF (220 mL), and the solution was cooled to -78°C. Solutions of MeMgBr (21.9 mL of a 3.0 M solution in Et₂O, 65.6 mmol), *sec*-BuLi (50.4 mL of a 1.3 M solution in cyclohexane, 65.6 mmol), and 1,4-cyclohexanedione mono-ethylene ketal (11.2 g, 71.5 mmol) in anhydrous THF (10 mL) were added sequentially at

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30-minute intervals. After the final addition, the reaction mixture was allowed to warm to room temperature. The reaction was quenched by the addition of 1N HCl (25 mL). The reaction mixture was diluted with EtOAc (500 mL), washed with saturated NaCl (250 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a mixture of 2 and 3, as a brown oil.

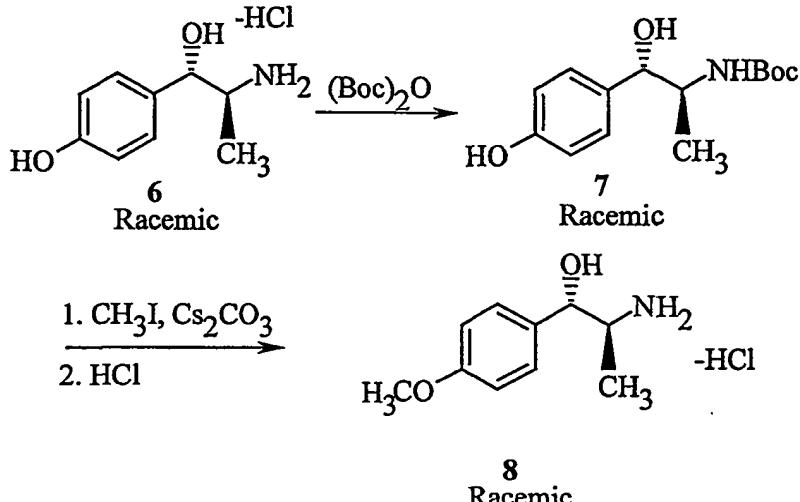
Step 3: The crude product from Step 2 was stirred in TFA (20 mL) at room temperature for 20 minutes. The red solution was poured into CHCl_3 (500 mL) and the organic layer was washed with H_2O (2×100 mL), saturated NaHCO_3 , and saturated NaCl, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by filtration through silica gel (eluent 9:1 $\text{CHCl}_3/\text{MeOH}$) gave a yellow oil. Crystallization from hexanes:EtOAc (3:1) gave 4 (8.1 g, 59%): ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.40 (d, $J = 1$ Hz, 1H), 7.30 (dd, $J = 8, 1$ Hz, 1H), 7.06 (d, $J = 8$ Hz, 1H), 6.11 (t, $J = 4$ Hz, 1H), 3.01 (d, $J = 2$ Hz, 2H), 2.83 (t, $J = 7$ Hz, 2H), 2.53 (m, 2H); CI MS (methane) (m/z): 230 [M + H]⁺.

Step 4: A mixture of 4 (3.5 g, 15.3 mmol) in a 3:2 mixture of EtOAc/EtOH (100 mL) and 10% Pd/C (0.5 g) was shaken under a H_2 atmosphere at 50 psi for 4 hours. The solution was filtered through Celite and concentrated under reduced pressure. Crystallization from hexanes:EtOAc (3:1) gave 6-(4-cyclohexanonyl)benzoxazolin-2-one 5 (3.45 g, 98%) as a white solid: mp 202-211°C; IR (KBr): 3339, 1777, 1713, 1618 cm^{-1} ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): δ 7.26 (s, 1H), 7.08 (d, $J = 8$ Hz, 1H), 7.01 (d, $J = 8$ Hz, 1H), 3.08 (tt, $J = 14, 4$ Hz, 1H), 2.63-2.51 (m, 2H), 2.24 (br d, $J = 14$ Hz, 2H), 2.07-2.02 (m, 2H), 1.95-1.85 (dd, $J = 14, 14, 14, 4$ Hz, 2H).

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Scheme 3

Preparation of α -(1-Aminoethyl)-4-methoxybenzyl alcohol hydrochloride 8



Step 1: To a stirred suspension of α -(1-aminoethyl)-4-hydroxybenzyl

5 alcohol hydrochloride 6 (5.0 g, 25 mmol), at 0°C, in CH_2Cl_2 (100 mL) was added Et₃N (10.6 mL, 76 mmol) followed by (Boc)₂O (5.9 g, 27 mmol). The reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was washed with 2N HCl (2 × 50 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 . The combined organic solutions were washed with saturated NaCl, dried (Na_2SO_4), and filtered. Concentration under reduced pressure gave 7 (7.01 g, 93%) which was used without further purification.

10 **Step 2:** To a solution of 7 (7.0 g, 23 mmol) in acetone (120 mL) was added K₂CO₃ (10.2 g, 73 mmol) followed by MeI (3.3 mL, 52 mmol). The reaction mixture was heated under reflux, under a N₂ atmosphere for 15 hours. After cooling to room temperature, the reaction mixture was filtered off, and the filtrate was concentrated under reduced pressure. Purification by flash chromatography (silica, 95:5 CH_2Cl_2 :MeOH) and (silica, 1:4 EtOAc:hexanes) afforded 3.0 g (41%) of desired material, which was used without further purification: ¹H NMR (500 MHz, CDCl₃): δ 7.25 (d, *J* = 7 Hz, 2H), 6.88 (d,

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J = 7 Hz, 2H), 4.80-4.75 (m, 1H), 4.60-4.54 (br s, 1H), 4.00-3.93 (br s, 1H), 3.80 (s, 3H), 3.12-3.04 (br s, 1H), 1.46 (s, 9H), 0.99 (d, *J* = 7 Hz, 3H).

Step 3: The carbamate 7 (3.0 g, 9.4 mmol) was stirred in HCl (25 mL of a 4 M solution in dioxane, 100 mmol) for 3 hours. The reaction mixture was then 5 diluted with Et₂O, which resulted in a white precipitate that was collected by filtration and dried to yield the desired amine 8 as the HCl salt (1.3 g, 54%): ¹H NMR (500 MHz, CD₃OD): δ 7.32 (d, *J* = 9 Hz, 2H), 6.94 (d, *J* = 9 Hz, 2H), 4.85 (s, 1H), 3.79 (s, 3H), 3.49-3.45 (m, 1H), 1.25 (d, *J* = 7 Hz, 3H).

Reductive Amination

10 General Methods

HCl salts were prepared by treatment of a MeOH solution of the amine with excess HCl in Et₂O (1.0 M). The salts were isolated either by filtration, if they precipitated directly from the etherial solution, or by first removal of the solvent under reduced pressure, and then crystallization (Et₂O/MeOH).

15 Purity was determined by reversed phase HPLC by the following methods:

Method A: column: YMC J'Sphere C18, ODS-M80, 150 × 4.6 mm, 4 μ; solvent A: 0.1% H₃PO₄ in H₂O; solvent B: 0.1% H₃PO₄ in CH₃CN; gradient: 10% to 100% B over 15 minutes; flow: 1 mL min⁻¹; detection: 210 nm.

Method B: column: YMC J'Sphere C18, ODS-M80, 150 × 4.6 mm, 4 μ; solvent A: 0.1% H₃PO₄ in H₂O; solvent B: 0.1% H₃PO₄ in MeOH; gradient: 10% to 100% B over 15 minutes; flow: 1 mL min⁻¹; detection: 210 nm.

Method C: column: Dynamax 300Å C18, 250 × 4.6 mm + guard, 5 μ; solvent A: 0.1% H₃PO₄ in H₂O; solvent B: 0.1% H₃PO₄ in CH₃CN; gradient: 10% to 100% B over 25 minutes; flow: 1 mL min⁻¹; detection: 215 nm.

25 Method D: column: Dynamax 300Å C18, 250 × 4.6 mm + guard, 5 μ; solvent A: 0.1% H₃PO₄ in H₂O; solvent B: 0.1% H₃PO₄ in MeOH; gradient: 10% to 100% B over 30 minutes; flow: 1 mL min⁻¹; detection: 215 nm.

Method E: column: YMC J'Sphere C18, ODS-M80, 150 × 4.6 mm, 4 μ;

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solvent A: 0.1% formic acid in H₂O; solvent B: 0.1% formic acid in MeOH;
gradient: 10% to 100% B over 20 minutes; flow: 1 mL min⁻¹; detection: 225 nm.

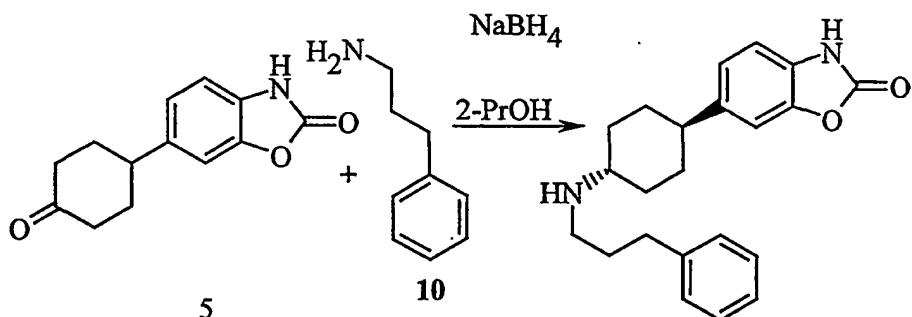
Existing Literature:

- 2-(4-Fluorophenoxy)ethylamine: Beilstein Registry Number: 1941572;
5 CAS #: 6096-89-5; Shtacher G., Taub W., *J. Med. Chem.*, 1966;9:197-203.
- 3-(4-Fluorophenyl)propylamine: Beilstein Registry Number: 7757402;
Fujimura K., Matsumoto J., Niwa M., Kobayashi T., Kawashima Y., et al., *Bioorg. Med. Chem.*, 1997;5:1675-1684.
- 3-Phenylsulfanylpropylamine: Beilstein Registry Number: 3695289;
10 CAS #: 34946-13-9; References to use of: Uher M., Jendrichovsky J., *Collect. Czech Chem. Commun.*, 1973;38:620-624. Tucker H., Coope J.F., *J. Med. Chem.*, 1978;21:769-773.
- 3-p-Tolylpropylamine: Beilstein Reference Number: 3235743; CAS #: 54930-39-1; v.Braun, Wirz, *Chem. Ber.*, 1927;60:107.
- 15 2-Methyl-3-phenylpropylamine: Beilstein Reference Number: 3237614;
CAS #: 77916-78-0; Belletire J.L., Fry D.F., *Synth. Commun.*, 1988;18:29-36.
- 3-Phenyl-prop-2-nylamine: Beilstein Reference Number: 2802264;
CAS #: 78168-74-8; Tomassy B., Zwierzak A., *Synth. Commun.*, 1988;28:1201-1214.
- 20 3-(4-Fluorophenyl)-propionic acid 2,5-dioxo-pyrrolidin-1-yl ester:
Beilstein Reference Number: 6657466; Shiosaki K., Lin C.W., Kopeka H.K.,
Craig R.A., Bruce, et al., *J. Med. Chem.*, 1992;35:2007-2014.
- 6-Bromo-5-methyl-3H-benzoxazol-2-one: Kalcheva V.B., Deligeorgiev
T.G., Zaneva D.A., *Dyes and Pigments*, 1991;15:275-278.
- 25 (4-Iodophenyl)dimethylamine: CAS #: 698-70-4; Yang S.G., Kim Y.H.,
Tetrahedron Lett., 1999;40:6051-6054.

EXAMPLE 1

6-[*trans*-4-(3-Phenylpropylamino)cyclohexyl]-3H-benzoxazol-2-one

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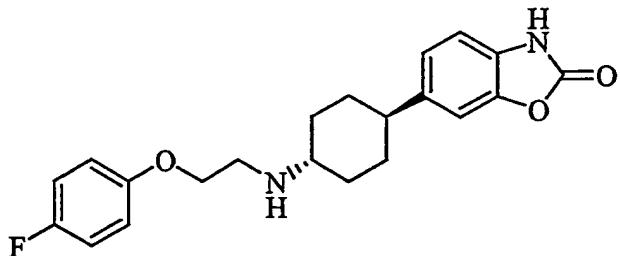
To a solution of ketone **5** (0.50 g, 2.0 mmol) in 2-propanol (30 mL) was added 3Å molecular sieves and 3-phenyl-1-propylamine **10** (0.39 g, 2.0 mmol). The reaction mixture was stirred for 4 hours. Sodium borohydride (0.11 g, 2.83 mmol) was added, and the reaction mixture was stirred overnight, quenched with MeOH, and concentrated under reduced pressure. Purification by flash chromatography (silica, 9.5:5:1 CH₂Cl₂:MeOH:NH₄OH) gave 6-[*trans*-4-(3-phenylpropylamino)-cyclohexyl]-3*H*-benzoxazol-2-one (0.30 g, 42%): mp 166-170°C; IR (KBr): 2933, 1761, 1653, 1582 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 9.09 (s, 1H), 7.30-7.19 (m, 6H), 7.03 (d, *J* = 9 Hz, 1H), 6.68 (d, *J* = 9 Hz, 1H), 2.66 (m, 1H), 2.55 (t, *J* = 8 Hz, 2H), 2.37 (tt, *J* = 10, 2 Hz, 1H), 1.98 (d, *J* = 10 Hz, 1H), 1.96 (d, *J* = 10 Hz, 1H), 1.76 (d, *J* = 3 Hz, 1H), 1.56 (m, 1H), 1.45 (m, 1H), 1.39 (m, 1H), 1.18-1.05 (m, 6H); CI-MS (methane) (*m/z*): 351 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₂H₂₆N₂O₂, 351.2072; found, 351.2178; HPLC: method A, 7.66 minutes (96.9%); method B, 14.14 minutes (97.7%); Anal. Calcd for C₂₂H₂₆N₂O₂·H₂O: C, 71.71; H, 7.66; N, 7.60. Found: C, 71.70; H, 7.62; N, 7.20.

The following compounds were prepared from the appropriate amines following the standard conditions. In some cases THF was used as a co-solvent to increase the solubility of the starting materials. The *trans*-isomer was usually formed as the major product. The *cis*-isomer was characterized when sufficient material was isolated.

EXAMPLE 2

6-{*trans*-4-[2-(4-Fluorophenoxy)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one

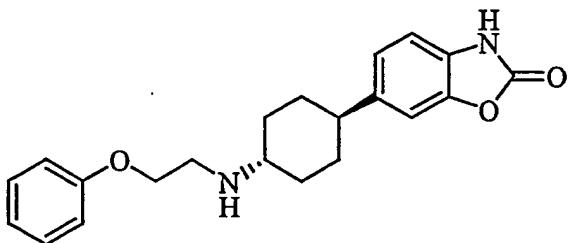
-37-



Coupling of ketone 5 and 2-(4-fluorophenoxy)ethylamine gave 6-{*trans*-4-[2-(4-fluorophenoxy)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one (0.14 g, 20%): mp 172-176°C; IR (KBr): 2931, 1759, 1654 cm⁻¹; ¹H NMR (500 MHz, CD₃OD): δ 7.10-6.90 (m, 7H), 4.08 (t, *J* = 5 Hz, 2H), 3.04 (t, *J* = 5 Hz, 2H), 2.62 (tt, *J* = 14, 2 Hz, 1H), 2.56 (tt, *J* = 14, 2 Hz, 1H), 2.11 (br d, *J* = 12 Hz, 2H), 1.92 (br d, *J* = 12 Hz, 2H), 1.57 (dddd, *J* = 12, 12, 12, 2 Hz, 2H), 1.33 (dddd, *J* = 12, 12, 12, 2 Hz, 2H); FAB-MS (*m/z*): 371 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₁H₂₃FN₂O₃, 371.1771; found, 371.1784; HPLC: method A, 10 7.51 minutes (96.4%); method B, 13.82 minutes (96.0%); Anal. Calcd for C₂₁H₂₃FN₂O₃·0.25 H₂O: C, 67.27; H, 6.32; N, 7.47. Found: C, 67.09; H, 6.40; N, 7.33.

EXAMPLE 3

6-[*trans*-4-(2-Phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one



15

Coupling of ketone 5 and 2-phenoxyethylamine gave 6-[*trans*-4-(2-phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one (0.18 g, 24%): mp 159-162°C; IR (KBr): 3262, 2926, 1759, 1654, 1600 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 7.34 (t, *J* = 2 Hz, 2H), 7.21 (s, 1H), 7.05-6.96 (m, 5H), 4.06 (t, *J* = 5 Hz, 2H), 2.98 (t, *J* = 5 Hz, 2H), 2.51 (tt, *J* = 11, 2 Hz, 1H), 2.49 (tt, *J* = 11, 2 Hz, 1H), 2.04 (br d, *J* = 11 Hz, 2H), 1.83 (br d, *J* = 11 Hz, 2H), 1.52 (dddd, *J* = 11, 11, 11, 2 Hz, 2H), 1.19 (dddd, *J* = 11, 11, 11, 2 Hz, 2H); API-MS (*m/z*):

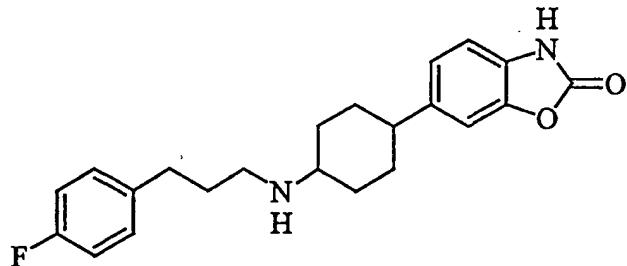
-38-

353 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₁H₂₄N₂O₃, 353.1865; found, 353.1868; HPLC: method A, 7.39 minutes (99.5%); method B, 13.49 minutes (100%); Anal. Calcd for C₂₁H₂₄N₂O₃·0.25H₂O: C, 70.67; H, 6.92; N, 7.85. Found: C, 70.43; H, 6.89; N, 7.49.

5

EXAMPLE 4

- (a) 6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one
 (b) 6-{*cis*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one



10 Coupling of ketone 5 and 3-(4-fluorophenyl)-1-propylamine gave (a) the *trans* isomer 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (HCl salt) (0.15 g, 21%): mp 293-307°C; IR (KBr): 2941, 1759 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.83 (broad s, 1H), 7.28 (t, *J* = 6, 3 Hz, 1H), 7.26 (s, 1H), 7.15 (t, *J* = 6, 3 Hz, 2H), 7.00 (m, 4H), 3.07 (m, 1H), 2.91 (m, 2H), 2.66 (t, *J* = 2 Hz, 2H), 2.50 (m, 1H), 2.13 (m, 2H), 1.92 (m, 2H), 1.85 (m, 3H), 1.49 (m, 4H); API-MS (*m/z*): 369 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₂H₂₅FN₂O₂, 369.1978; found, 369.1980; HPLC: method A, 7.78 minutes (99.8%); method B, 14.29 minutes (100%); Anal. Calcd for C₂₂H₂₅FN₂O₂·HCl·0.5H₂O: C, 63.84; H, 6.57; N, 6.77. Found: C, 63.64; H, 6.50; N, 6.57 and

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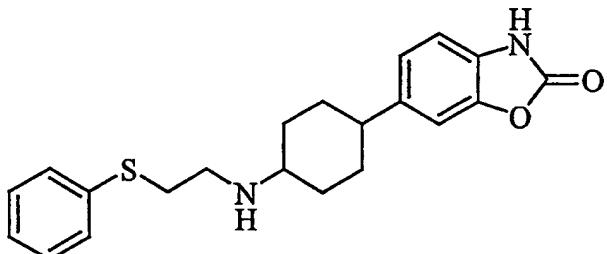
15 (b) the *cis* isomer 6-{*cis*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (750 mg, 35%): ¹H NMR (500 MHz, CD₃OD): δ 7.27-7.22 (m, 3H), 7.13 (d, *J* = 8 Hz, 1H), 7.05-7.10 (m, 3H), 3.43-3.39 (m, 1H), 3.08-3.04 (m, 2H), 2.85-2.80 (m, 1H), 2.76-2.72 (m, 2H), 2.08-1.81 (m, 10H).

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EXAMPLE 5

- (a) 6-[*trans*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one
- (b) 6-[*cis*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one



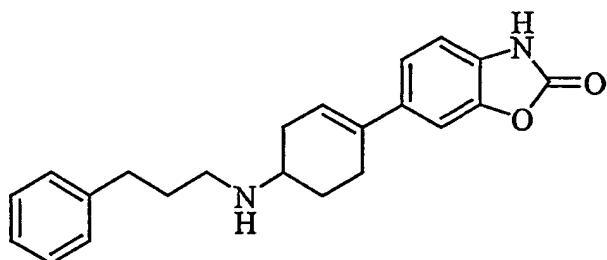
5 Coupling of ketone 5 and 2-phenylsulfanylethylamine gave (a) the *trans*-isomer 6-[*trans*-4-(2-phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one isolated as the HCl salt (0.13 g, 14%): mp 241-243°C; IR (KBr): 2940, 2858, 1762 cm⁻¹; ¹H NMR (500 MHz, CD₃OD): δ 7.50-7.30 (m, 5H), 7.11 (s, 1H), 7.03-6.98 (m, 2H) 3.30 (s, 4H), 3.24 (tt, *J* = 14, 2 Hz, 1H), 2.60 (tt, *J* = 14, 2 Hz, 1H), 2.18 (br d, *J* = 12 Hz, 2H), 1.99 (br d, *J* = 12 Hz, 2H), 1.57 (dd, *J* = 12, 12, 12, 2 Hz, 4H); API -MS (*m/z*): 369 [M + H]⁺ HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₁H₂₄N₂O₂S, 369.1636; found, 369.1638; HPLC: method A, 7.86 minutes (98.0%); method B, 14.46 minutes (99.1%); Anal. Calcd for C₂₁H₂₄N₂O₂S·HCl·0.25 H₂O: C, 61.60; H, 6.28; N, 6.84. Found: C, 61.60; H, 6.16; N, 6.68; and

10 (b) The *cis*-isomer 6-[*cis*-4-(2-phenylsulfanylethylamino)-cyclohexyl]-3*H*-benzoxazol-2-one was isolated as the HCl salt (0.14 g, 9%): mp 182-190°C; IR (KBr): 2939, 1762 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.80 (br s, 2H), 7.44-6.98 (m, 8H), 3.37-3.28 (m, 4H), 3.15-3.13 (m, 1H), 2.80-2.75 (m, 1H), 1.95-1.63 (m, 8H); API-MS (*m/z*): 369 [M + H]⁺; HPLC: method A, 7.92 minutes (98.4%); method B, 14.47 minutes (98.2%); Anal. Calcd for C₂₁H₂₄N₂O₂S·HCl·0.50H₂O: C, 60.93; H, 6.33; N, 6.77. Found: C, 60.91; H, 6.37; N, 6.69.

EXAMPLE 6

25 6-[4-(3-Phenylpropylamino)cyclohex-1-enyl]-3*H*-benzoxazol-2-one

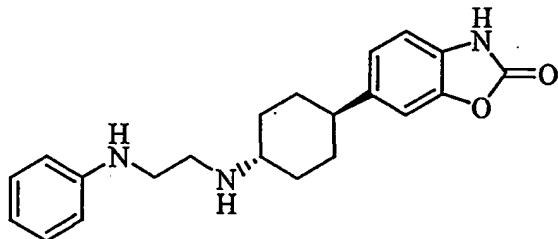
-40-



To a solution of ketone 3 (0.50 g, 2.0 mmol) in 2-propanol (30 mL) was added 3Å molecular sieves and 3-phenyl-1-propylamine (**10**) (0.39 g, 2.0 mmol). The reaction mixture was stirred for 4 hours. Sodium borohydride (0.11 g, 5 2.83 mmol) was added, and the reaction mixture was stirred overnight, quenched with MeOH, and concentrated under reduced pressure. Purification by flash chromatography (silica, 9.5:5:1 CH₂Cl₂:MeOH:NH₄OH) gave 6-[4-(3-phenylpropylamino)cyclohexyl]-3H-benzoxazol-2-one (0.12 g, 21%): mp 293-295°C; IR (KBr): 2950, 1779, 1496 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 7.32 (s, 1H), 7.30-7.17 (m, 6H), 7.00 (d, J = 1 Hz, 1H), 6.03 (m, 1H), 2.79 (m, 1H), 2.65 (m, 4H), 2.50 (m, 4H), 1.94 (m, 2H), 1.75 (m, 2H), 1.47 (m, 2H); API-MS (m/z): 349 [M + H]⁺; HRMS-API (m/z): [M + H]⁺ calcd for C₂₂H₂₄N₂O₂, 349.1916; found, 349.1917; HPLC: method A, 7.67 minutes (97.9%); method B, 14.06 minutes (99.8%); Anal. Calcd for C₂₂H₂₄N₂O₂·0.8H₂O: C, 72.82; H, 10 7.11; N, 7.72. Found: C, 72.55; H, 7.13; N, 7.34.

EXAMPLE 7

6-[*trans*-4-(2-Phenylaminoethylamino)cyclohexyl]-3H-benzoxazol-2-one



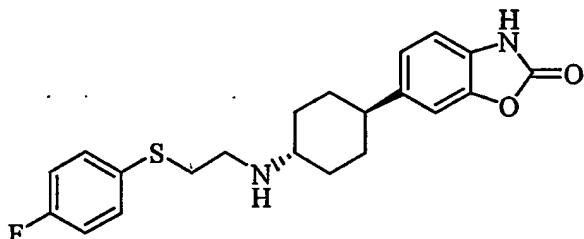
Coupling of ketone **5** and 2-(4-aminophenyl)ethylamine gave 6-[*trans*-4-(2-phenylaminoethylamino)cyclohexyl]-3H-benzoxazol-2-one (0.18 g, 26%): mp 293-295°C; IR (KBr): 2950, 1779, 1496 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 7.16 (s, 1H), 7.09 (t, J = 6 Hz, 2H), 7.01 (dd, J = 6, 1 Hz, 2H), 6.98-6.53 (m,

-41-

3H), 5.51 (br s, 1H), 3.18 (m, 2H), 2.86 (m, 2H), 2.64 (m, 1H), 2.49 (m, 1H),
 2.01 (br d, $J = 9$ Hz, 2H), 1.81 (br d, $J = 9$ Hz, 2H), 1.47 (dddd, $J = 9, 9, 9, 1$ Hz,
 2H), 1.24 (dddd, $J = 9, 9, 9, 1$ Hz, 2H); API-MS (m/z): 352 [M + H]⁺; HPLC:
 method A, 7.36 minutes (98.2%); method B, 13.46 minutes (98.5%); Anal. Calcd
 5 for C₂₁H₂₅N₃O₂: C, 71.77; H, 7.17; N, 11.96. Found: C, 65.64; H, 7.09; N,
 10.08.

EXAMPLE 8

6-{*trans*-4-[2-(4-Fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one



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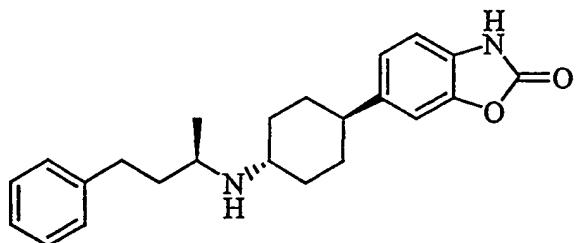
Coupling of ketone 5 and 2-(4-fluorophenylsulfanyl)ethylamine gave
 6-{*trans*-4-[2-(4-fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one isolated as the HCl salt (0.10 g, 5%): mp 254–256°C; IR (KBr): 2933, 2809,
 1775 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.91 (br s, 2H), 7.53–7.50 (m,
 15 2H), 7.25–7.20 (m, 3H), 7.18–7.14 (m, 2H) 3.30–3.23 (m, 2H), 3.10–3.07 (m, 3H),
 2.52–2.50 (m, 1H), 2.11–2.05 (m, 2H), 1.85–1.84 (m, 2H), 1.51–1.42 (m, 4H); API-
 MS (m/z): 387 [M + H]⁺; HPLC: method A, 14.65 minutes (>99%); Anal. Calcd
 for C₂₁H₂₃FN₂O₂S·HCl: C, 59.64; H, 5.72; N, 6.62. Found: C, 59.49; H, 5.73;
 N, 6.47.

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EXAMPLE 9

6-{*trans*-4-[*(R*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one

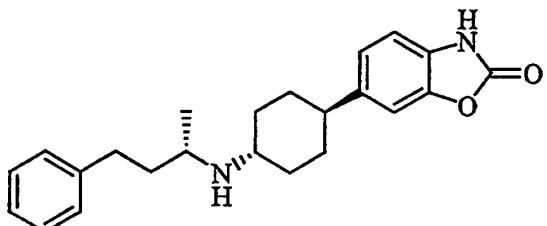
-42-



Coupling of ketone 5 and (*R*)-4-phenyl-2-butylamine gave 6-{*trans*-4-[*(R*)-1-methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one isolated as an HCl salt (0.12 g, 21%): mp 291-304°C; IR (KBr): 2945, 1752, 1623 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 8.67 (s, 1H), 7.35-7.30 (m, 5H), 7.22 (s, 1H), 6.98 (m, 2H), 3.26 (m, 4H), 2.74-2.61 (m, 2H), 2.14 (m, 2H), 1.93-1.74 (m, 3H), 1.53 (m, 4H), 1.33 (d, *J* = 6 Hz, 3H); API-MS (*m/z*): 365 [M + H]⁺; HPLC: method A, 8.11 minutes (97.7%); method B, 14.96 minutes (99.7%); [∞]_D²⁵ +17.5°(*c* 0.08, MeOH); Anal. Calcd for C₂₃H₂₈N₂O₂·HCl·0.5H₂O: C, 67.39; H, 7.38; N, 6.83. Found: C, 67.38; H, 7.17; N, 6.71.

EXAMPLE 10

6-{*trans*-4-[*(S*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one



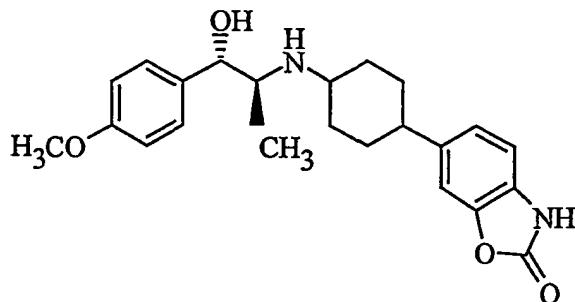
Coupling of ketone 5 and and (*S*)-4-phenyl-2-butylamine gave 6-{*trans*-4-[*(S*)-1-methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one (0.12 g, 21%): mp 174-176°C; IR (KBr): 2925, 1761, 1654, 1583 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.23-7.12 (m, 5H), 7.11 (s, 1H), 7.09 (m, 2H), 2.71 (tt, *J* = 10, 2 Hz, 1H), 2.56 (t, *J* = 5 Hz, 2H), 2.48 (tt, *J* = 10, 2 Hz, 1H), 1.87-1.70 (m, 2H), 1.63 (d, *J* = 7 Hz, 2H), 1.58 (m, 1H), 1.57-1.36 (m, 4H), 1.11-1.04 (m, 4H), 1.01 (d, *J*= 9 Hz, 3H); API-MS (*m/z*): 365 [M + H]⁺; HPLC:

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method B, 14.91 minutes (98.6%); $[\alpha]^{25}_D -8.0^\circ$ (*c* 0.125, MeOH); Anal. Calcd for C₂₃H₂₈N₂O₂: C, 75.79; H, 7.74; N 7.69. Found: C, 75.48; H, 8.02; N, 7.30.

EXAMPLE 11

- 5 (a) 6-{*trans*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]-cyclohexyl}-3*H*-benzoxazol-2-one
- (b) 6-{*cis*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]-cyclohexyl}-3*H*-benzoxazol-2-one



10 Coupling of ketone 5 and α-(1-aminoethyl)-4-methoxybenzyl alcohol hydrochloride 8 gave (a) the *trans*-isomer 6-{*trans*-4-[(1*S*,2*S*)-2-hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one isolated as the HCl salt (0.18 g, 12%): mp 241-249°C; IR (KBr): 3300, 2943, 1758 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.52 (br s, 2H), 7.33 (d, *J* = 9 Hz, 2H), 7.19 (s, 1H), 7.14-7.00 (m, 2H), 6.95 (d, *J* = 9 Hz, 2H), 6.05 (br s, 1H), 5.09 (br s, 1H), 3.76 (s, 3H), 3.47 (br s, 1H), 3.23-3.20 (m, 1H), 2.60-2.46 (m, 1H), 2.31-2.08 (m, 2H), 1.91-1.87 (m, 2H), 1.65-1.50 (m, 4H), 0.97 (d, *J* = 7 Hz, 3H); CI-MS (methane) (*m/z*): 397 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₃H₂₈N₂O₄, 397.2127; found, 397.2126; HPLC: method A, 6.69 minutes (97.8%); method B, 11.90 minutes (99.3%); Anal. Calcd for C₂₃H₂₈N₂O₄·HCl·0.50H₂O: C, 62.51; H, 6.84; N, 6.34. Found: C, 62.63; H, 6.78; N, 6.25; and

15 (b) the *cis*-isomer 6-{*cis*-4-[(1*S*,2*S*)-2-hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one was isolated as the HCl salt (0.068 g, 4%): mp 195-197°C; IR (KBr): 2940, 1758 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.40-8.25 (m, 2H), 7.37-7.32 (m, 3H), 7.13 (br d, *J* = 8 Hz, 1H),

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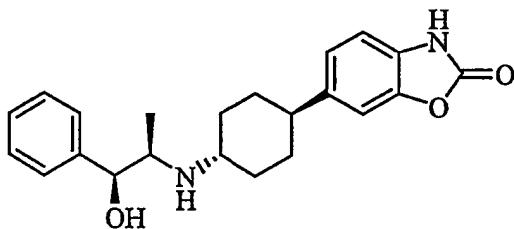
-44-

7.03 (d, $J = 8$ Hz, 1H), 6.94 (d, $J = 9$ Hz, 2H), 6.05-6.03 (m, 1H), 5.16-5.15 (m, 1H), 3.75 (s, 3H), 3.56-3.41 (m, 2H), 2.73-2.79 (m, 1H), 2.12-1.78 (m, 6H), 1.73-1.65 (m, 2H), 0.99 (d, $J = 7$ Hz, 3H); CI-MS (methane) (m/z): 397 [M + H]⁺; HRMS-API (m/z): [M + H]⁺ calcd for C₂₃H₂₈N₂O₄, 397.2127; found, 397.2125;

5 HPLC: method A, 7.04 minutes (96.4%); method B, 12.44 minutes (96.8%); Anal. Calcd for C₂₃H₂₈N₂O₄·HCl·0.25H₂O: C, 63.15; H, 6.80; N, 6.40. Found: C, 63.02; H, 6.69; N, 6.29.

EXAMPLE 12

10 6-{*trans*-4-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one

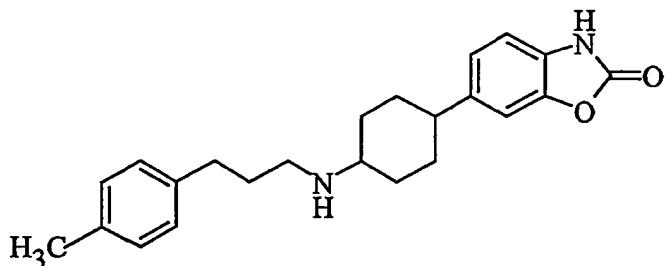


Coupling of ketone 5 and (1*S*,2*R*)-(+) -norephedrine hydrochloride gave the *trans*-isomer 6-{*trans*-4-[(1*S*,2*R*)-2-hydroxy-1-methyl-2-phenylethylamino]-cyclohexyl}-3*H*-benzoxazol-2-one isolated as the HCl salt (0.12 g, 21%): mp 251-256°C; IR (KBr): 2942, 1754, 1624 cm⁻¹; ¹H NMR (300 MHz, DMSO-d₆): δ 8.59 (s, 2H), 7.44-7.30 (m, 5H), 7.20 (s, 1H), 7.02-6.98 (m, 2H), 6.17 (d, $J = 4$ Hz, 1H), 5.15 (m, 1H), 3.52 (m, 1H), 2.58 (m, 1H), 2.47 (m, 1H), 2.37 (m, 1H), 1.88 (m, 2H), 1.62 (m, 4H), 0.97 (d, $J = 6$ Hz, 3H); API-MS (m/z): 367 [M + H]⁺; HPLC: method A, 7.59 minutes (97.9%); method B, 14.18 minutes (98.5%); Anal. Calcd for C₂₂H₂₆N₂O₃·HCl: C, 62.77; H, 6.94; N, 6.66. Found: C, 62.59; H, 6.64; N, 6.39.

EXAMPLE 13

- (a) 6-[*cis*-4-(3-p-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one
- (b) 6-[*trans*-4-(3-p-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one

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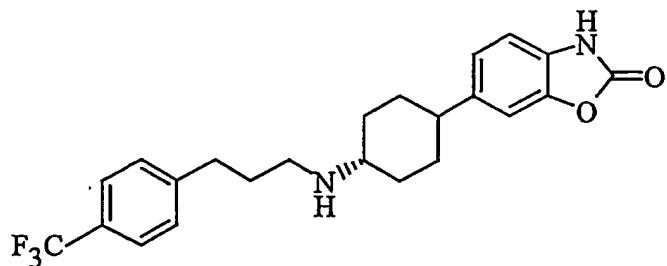


Coupling of ketone 5 and 3-*p*-tolylpropylamine gave (a) the *cis*-isomer 6-[*cis*-4-(3-*p*-tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one isolated as the HCl salt (0.12 g, 7%): mp 263-265°C; IR (KBr): 2941, 1765 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.64 (br s, 2H), 7.36-7.35 (m, 1H), 7.12-6.99 (m, 6H), 3.33-3.29 (m, 1H), 2.90-2.96 (m, 2H), 2.66-2.60 (m, 3H), 2.27 (s, 3H), 2.01-1.89 (m, 6H), 1.77-1.69 (m, 2H), 1.65-1.59 (m, 2H); CI MS (methane) (*m/z*): 365 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₃H₂₈N₂O₂, 365.2229; found, 365.2228; HPLC: method A, 7.14 minutes (95.2%); method B, 13.08 minutes (96.6%); Anal. Calcd for C₂₃H₂₈N₂O₂·HCl·0.50H₂O: C, 68.13; H, 7.33; N, 6.91. Found: C, 68.33; H, 7.27; N, 6.92; and (b) the *trans*-isomer 6-[*trans*-4-(3-*p*-tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one was isolated as the HCl salt (0.27 g, 16%): mp 295-301°C; IR (KBr): 2942, 1763 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.79 (m, 2H), 7.17 (br s, 1H), 7.13-7.11 (m, 4H), 7.02-6.97 (m, 2H), 3.05 (br s, 1H), 2.92-2.89 (m, 2H), 2.63 (t, *J* = 8 Hz, 2H), 2.53-2.50 (m, 1H), 2.27 (s, 3H), 2.16-2.10 (m, 2H), 1.95-1.85 (m, 4H), 1.55-1.46 (m, 4H); CI-MS (methane) (*m/z*): 365 [M + H]⁺; HPLC: method A, 7.02 minutes (96.5%); method B, 13.11 minutes (98.8%); Anal. Calcd for C₂₃H₂₈N₂O₂·HCl: C, 68.90; H, 7.29; N, 6.99. Found: C, 68.78; H, 7.21; N 6.87.

EXAMPLE 14

6-{*trans*-4-[3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one

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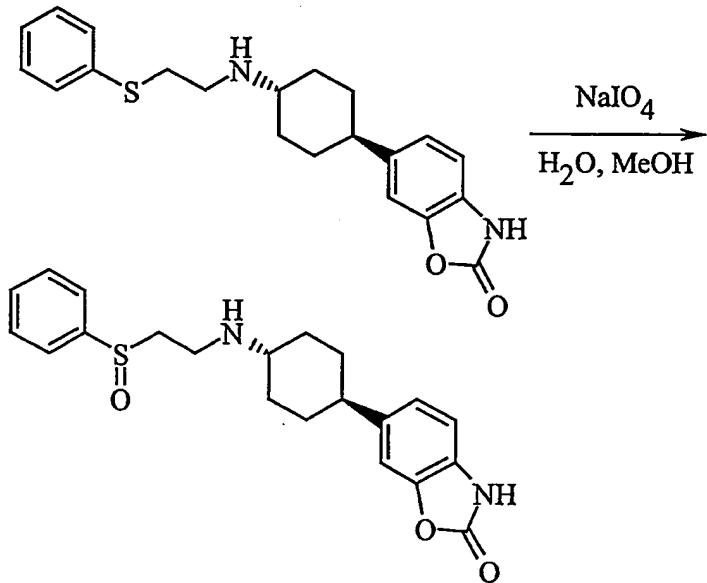


Coupling of ketone 5 and 3-(4-trifluoromethylphenyl)-1-propylamine gave 6-{*trans*-4-[3-(4-trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one isolated as an HCl salt (0.78 g, 33%): mp 285-295°C; IR (KBr): 2945,

5 1766 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.47 (s, 1H), 8.81 (s, 2H),
7.68 (d, *J* = 8 Hz, 2H), 7.49 (d, *J* = 8 Hz, 2H), 7.17 (s, 1H), 7.20-6.97 (m, 2H),
3.10-3.02 (m, 1H), 2.98-2.91 (m, 2H), 2.80 (t, *J* = 8 Hz, 2H), 2.57-2.50 (m, 1H),
2.18-2.11 (m, 2H), 2.01-1.95 (m, 2H), 1.90-1.84 (m, 2H), 1.51 (m, 4H); CI-MS
(*m/z*): 419 [M + H]⁺; HPLC: method A, 6.87 minutes (97.7%); Anal. Calcd for
10 C₂₃H₂₅F₃N₂O₂·HCl: C, 60.73; H, 5.76; N, 6.16. Found: C, 60.63; H, 5.97; N,
6.04.

EXAMPLE 15

6-[*trans*-4-(2-Benzenesulfinylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one

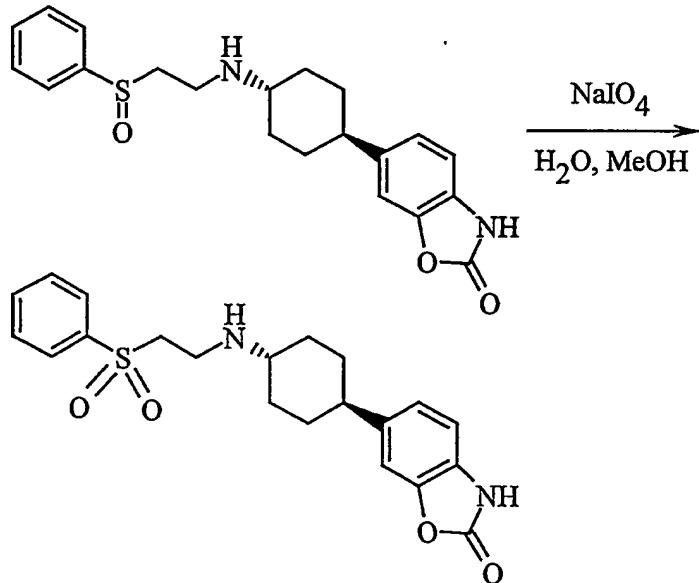


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To a stirred, ice-cold, suspension of NaIO₄ (0.13 g, 0.62 mmol) in H₂O (1.2 mL) was added 6-[*trans*-4-(2-phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one (0.25 g, 0.62 mmol). The viscous reaction mixture was diluted with H₂O (1.5 mL), warmed to room temperature, and then further diluted with MeOH (15 mL). After 21 hours, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography (silica, 89:10:1 CH₂Cl₂:MeOH:NH₄OH) gave the free base of 6-[*trans*-4-(2-benzenesulfinylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one, which was converted to the HCl salt (0.13 g, 49%): mp 107-110°C; IR (KBr): 2936, 2783, 1768, cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 9.03 (br s, 2H), 7.74-7.60 (m, 5H), 7.16 (s, 1H), 6.99-6.97 (m, 2H), 3.48-3.43 (m, 1H), 3.33-3.29 (m, 1H), 3.18-3.04 (m, 4H), 2.54-2.52 (m, 2H), 1.86-1.84 (m, 2H), 1.51-1.44 (m, 4H); API-MS (*m/z*): 385 [M + H]⁺; HPLC: method A, 7.01 minutes (98.1%); method B, 12.83 minutes (99.2%); Anal. Calcd for C₂₁H₂₄N₂O₃S·HCl·1.25 H₂O: C, 56.88; H, 6.25; N, 6.32. Found: C, 56.86; H, 6.18; N, 6.22.

EXAMPLE 16

6-[*trans*-4-(2-Benzenesulfonylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one



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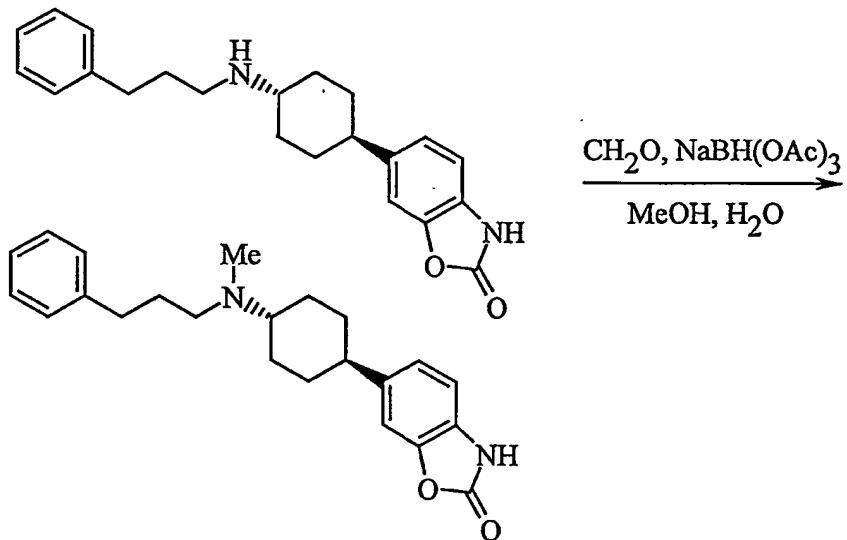
To a stirred suspension of NaIO₄ (0.30 g, 1.4 mmol) in a mixture of H₂O (5 mL) and MeOH (5 mL) was added 6-[*trans*-4-(2-phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one (0.19 g, 0.47 mmol). After 48 hours, a second portion of NaIO₄ (0.20 g, 0.93 mmol) was added, and stirring was continued
5 overnight. The reaction mixture was heated at 60°C for 6 hours, then cooled to room temperature and concentrated under reduced pressure. The solids were suspended in a 2:1 mixture of MeOH and CH₂Cl₂ and the solution filtered. The filtrate was concentrated under reduced pressure. Purification by flash chromatography (silica, 50:49:1 acetone:CH₂Cl₂:MeOH) gave the free base
10 6-[*trans*-4-(2-benzenesulfonylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one, which was converted to the HCl salt (0.050 g, 24%): mp 202-208°C; IR (KBr): 3448, 2939, 1763 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.97 (br s, 2H), 7.98-7.71 (m, 5H), 7.16 (s, 1H), 6.99-6.98 (m, 2H), 3.77-3.74 (m, 1H), 3.25-3.23 (m, 1H), 3.21-3.20 (m, 4H), 2.09-2.04 (m, 2H), 1.90-1.40 (m, 2H), 1.52-1.40 (m, 4H);
15 CI-MS (methane) (*m/z*): 401 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₁H₂₄N₂O₄S, 401.1535; found, 401.1535; HPLC: method A, 6.34 minutes (97.3%); method B, 11.06 minutes (99.1%); Anal. Calcd for C₂₁H₂₄N₂O₄S·HCl·0.50H₂O: C, 56.56; H, 5.88; N, 6.28. Found: C, 56.29; H, 5.65; N, 6.13.

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EXAMPLE 17

6-{*trans*-4-[Methyl(3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one

-49-



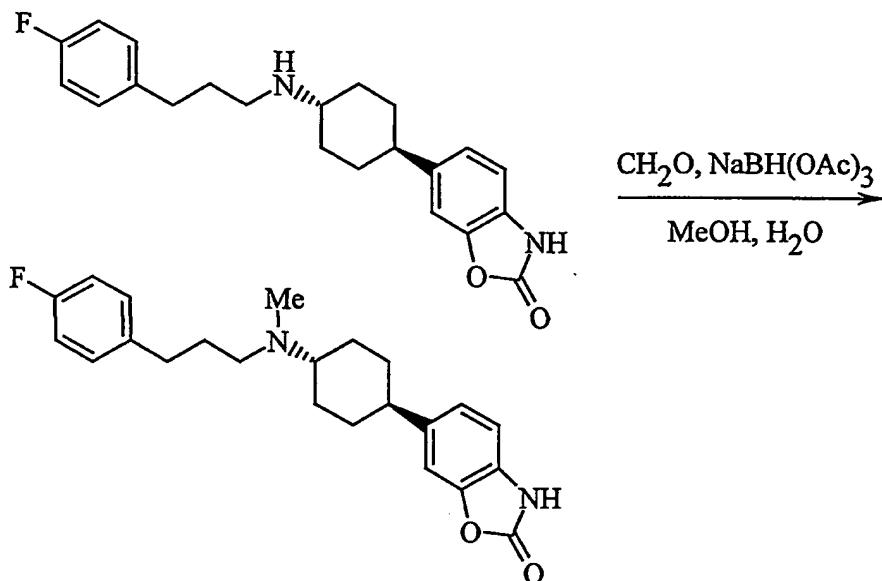
To a stirred solution of 6-[*trans*-4-(3-phenylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one (263 mg, 0.750 mmol) in MeOH (10 mL) was added H₂O (0.5 mL) and *p*-formaldehyde (113 mg, 3.75 mmol). After stirring the reaction mixture for 3 hours, NaBH(OAc)₃ was added, and stirring was continued for 12 hours. Solid NaOH was added to give a clear solution, which was then concentrated under reduced pressure. Purification by flash chromatography (silica, 95:4:1 CH₂Cl₂:MeOH:NH₄OH) gave 6-{*trans*-4-[methyl(3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (160 mg, 59%), as a white solid: mp 58-62°C; IR (KBr): 2929, 1774 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.97 (br s, 1H), 7.26-7.12 (m, 6H), 6.99-6.98 (m, 2H), 2.63 (m, 2H), 2.57 (t, *J* = 7 Hz, 2H), 2.56 (m, 1H), 2.38 (m, 2H), 2.18 (s, 3H), 1.78 (m, 2H), 1.68 (m, 2H), 1.37 (m, 2H), 1.27 (m, 2H); CI-MS (methane) (*m/z*): 365 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₃H₂₈N₂O₂, 365.2229; found, 365.2231; HPLC: method A, 5.95 minutes (95.3%); method B, 10.12 minutes (97.6%); Anal. Calcd for C₂₃H₂₈N₂O₂·0.25H₂O: C, 74.87; H, 7.79; N, 7.59. Found: C, 74.77; H, 7.71; N, 7.81.

EXAMPLE 18

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one

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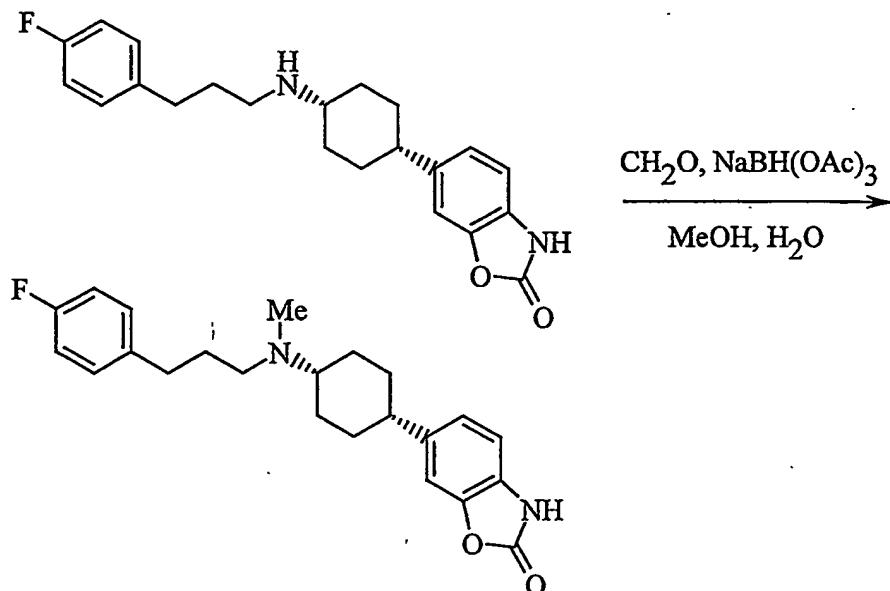


Coupling of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (519 mg, 1.40 mmol) and *p*-formaldehyde (210 mg, 1.00 mmol), following the procedure described in Example 17, gave 6-(*trans*-4-
5 {[3-(4-fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one
(135 mg, 26%), as a white solid: mp 62-65°C; IR (KBr): 2930, 1774, 1654,
1509 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.24-6.94 (m, 8H), 2.57 (m, 3H),
2.39 (m, 1H), 2.36 (m, 4H), 2.18 (s, 3H), 1.82 (m, 2H), 1.77 (m, 2H), 1.44 (m,
2H), 1.35 (m, 2H); CI-MS (methane) (*m/z*): 383 [M + H]⁺ HRMS-API (*m/z*):
10 [M + H]⁺; calcd for C₂₃H₂₇FN₂O₂, 383.2135; found, 383.2133; HPLC: method
A, 6.04 minutes (95.7%); method B, 10.73 minutes (96.8%); Anal. Calcd for
C₂₃H₂₇FN₂O₂·0.75H₂O: C, 69.76; H, 7.25; N, 7.07. Found: C, 69.53; H, 6.97;
N, 7.23.

EXAMPLE 19

15 6-(*cis*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-
one

-51-



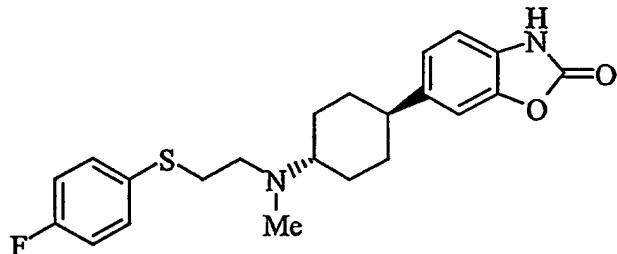
Coupling of 6-{*cis*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (519 mg, 1.40 mmol) and *p*-formaldehyde (210 mg, 1.00 mmol), following the procedure described in Example 17, gave 6-(*cis*-4-{[3-(4-fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (600 mg, 78%), as an off-white glass: IR (KBr): 2944, 1770 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 10.05 (s, 1H), 7.41 (s, 1H), 7.31-7.26 (m, 2H), 7.16-7.09 (m, 3H), 6.99 (d, *J* = 8 Hz, 1H), 3.38-3.30 (m, 1H), 3.15-3.07 (m, 1H), 3.07-2.98 (m, 1H), 2.81-2.77 (m, 1H), 2.70 (d, *J* = 5 Hz, 3H), 2.65-2.49 (m, 2H), 2.13-1.66 (m, 10H); ESI-MS (*m/z*): 383 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₃H₂₇FN₂O₂, 383.2135; found, 383.2132; HPLC: method A, 5.88 minutes (98.7%); method B, 10.97 minutes (98.6%); Anal. Calcd for C₂₃H₂₇FN₂O₂·HCl·0.25H₂O: C, 65.24; H, 6.78; N, 6.62. Found: C, 65.41; H, 6.97; N, 6.72.

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EXAMPLE 20

6-{*trans*-4-[2-(4-Fluorophenylsulfanyethyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one

-52-

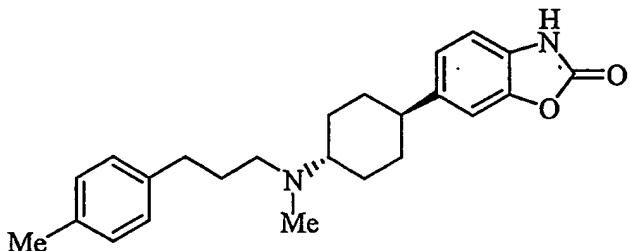


6-{*trans*-4-[2-(4-Fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one (197 mg, 0.51 mmol) was coupled with *p*-formaldehyde (76 mg, 2.5 mmol), following the procedure described in Example 17, except CH₂Cl₂ (5 mL) was added. Formation of the HCl salt gave 6-{*trans*-4-[2-(4-fluorophenylsulfanylethyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one (154 mg, 69%), as a white solid: mp 213-217°C; IR (KBr): 2942, 1770, 1492 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.49 (s, 1H), 10.64 (br s, 1H), 7.56-7.51 (m, 2H), 7.25-7.21 (m, 2H), 7.14 (s, 1H), 7.00 (br s, 2H), 3.50-3.31 (m, 3H), 3.31-3.15 (m, 2H), 2.72 (d, *J* = 5 Hz, 3H), 2.54-2.50 (m, 1H), 2.14-2.02 (m, 2H), 1.90-1.85 (m, 2H), 1.68-1.49 (m, 4H); CI-MS (methane) (*m/z*): 401 [M + H]⁺; HPLC: method A, 5.95 minutes (98.1%); Anal. Calcd for C₂₂H₂₅FN₂O₂S·HCl: C, 60.47; H, 6.00; N, 6.41. Found: C, 60.17; H, 6.00; N, 7.34.

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EXAMPLE 21

6-{*trans*-4-[Methyl-3-(*p*-Tolylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one



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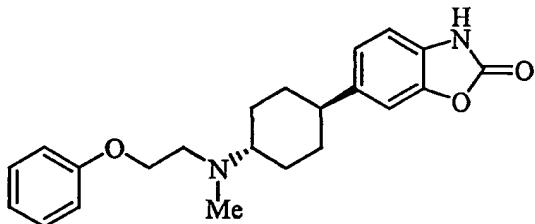
6-{*trans*-4-(3-*p*-Tolylpropylamino)cyclohexyl}-3*H*-benzoxazol-2-one (300 mg, 0.82 mmol) was coupled with *p*-formaldehyde (120 mg, 4.1 mmol) following the procedure described in Example 17 except CH₂Cl₂ (8 mL) was added. Also, additional NaBH(OAc)₃ and *p*-formaldehyde were added at intervals to drive the reaction to completion. Formation of the HCl salt gave 6-{*trans*-4-

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[methyl-3-(*p*-tolylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (224 mg, 66%), as a white solid: mp 213-225°C; IR (KBr): 2944, 1771, 1498, 1451 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.48 (s, 1H), 9.85 (br s, 1H), 7.16-7.10 (m, 5H), 7.00 (br s, 2H), 3.32-3.26 (m, 1H), 3.19-3.11 (m, 1H), 3.04-2.97 (m, 1H), 2.70 (d, *J* = 4 Hz, 3H), 2.65-2.50 (m, 3H), 2.28 (s, 3H), 2.12-2.02 (m, 2H), 2.02-1.94 (m, 2H), 1.94-1.88 (m, 2H), 1.68-1.50 (m, 4H); CI-MS (methane) (*m/z*): 379 [M + H]⁺; calcd for C₂₄H₃₀N₂O₂, 379.2385; found, 379.2397; HPLC: method A, 6.45 minutes (99.4%); method B, 15.17 minutes (>99%); Anal. Calcd for C₂₄H₃₀N₂O₂·HCl·0.5H₂O: C, 67.99; H, 7.61; N, 6.61. Found: C, 67.96; H, 7.57; N, 6.84.

EXAMPLE 22

6-{*trans*-4-[Methyl(2-phenoxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one



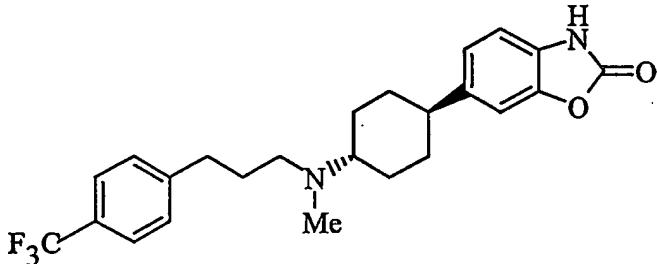
15 6-*trans*-[4-(2-Phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one (250 mg, 0.71 mmol) was coupled with *p*-formaldehyde (100 mg, 3.5 mmol) following the procedure described in Example 17, except CH₂Cl₂ (10 mL) was added. Also, additional NaBH(OAc)₃ and NaBH₄ were added at intervals to drive the reaction to completion. Formation of the HCl salt gave 6-{*trans*-4-[methyl(2-phenoxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (219 mg, 77%), as a white solid: mp 277-285°C; IR (KBr): 2939, 1769, 1496 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.48 (s, 1H), 10.00 (br s, 1H), 7.37-7.32 (m, 2H), 7.17 (s, 1H), 7.03-6.99 (m, 5H), 4.43-4.38 (m, 2H), 3.69-3.61 (m, 1H), 3.50-3.37 (m, 2H), 2.84 (d, *J* = 4 Hz, 3H), 2.61-2.52 (m, 1H), 2.22-2.12 (m, 2H), 1.99-1.91 (m, 2H), 1.72-1.50 (m, 4H); CI-MS (methane) (*m/z*): 367 [M + H]⁺; calcd for C₂₂H₂₆N₂O₃, 367.2021; found, 367.2018; HPLC: method A, 5.48 minutes (97.2%); method B, 12.81 minutes (98.0%); Anal. Calcd for

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$C_{22}H_{26}N_2O_3 \cdot HCl \cdot 0.1NH_4Cl$: C, 64.72; H, 6.76; N, 7.20. Found: C, 64.52; H, 6.86; N, 7.34.

EXAMPLE 23

5 6-{*trans*-4-[Methyl-3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one



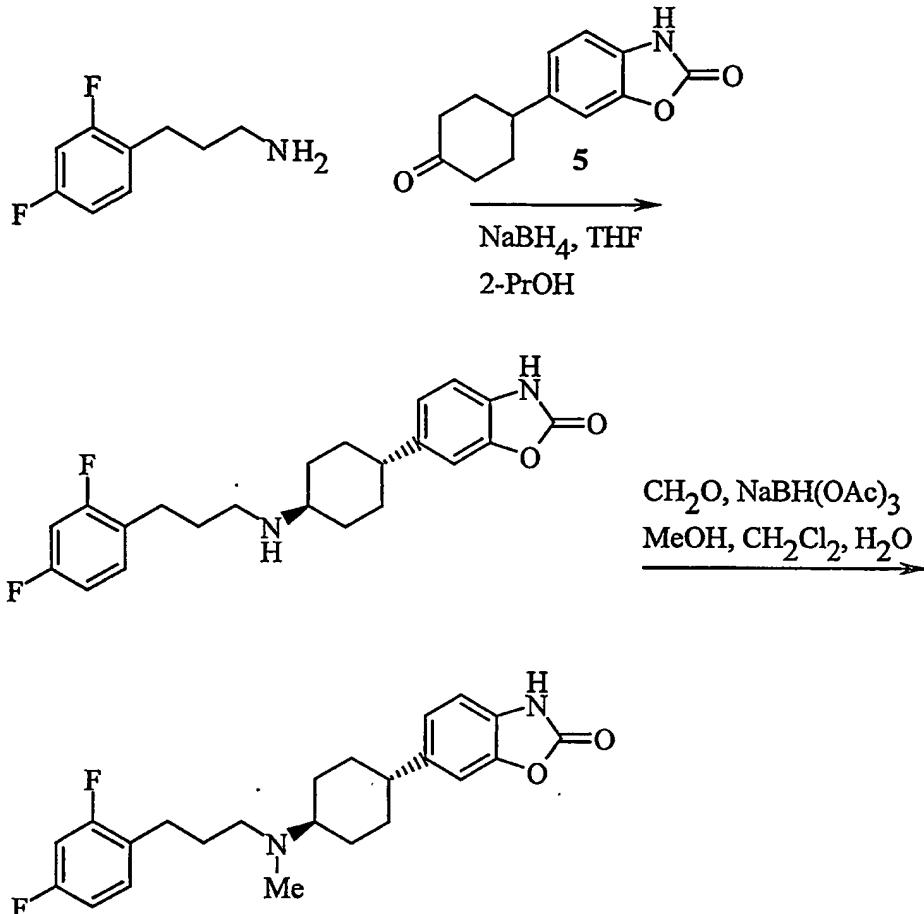
10 6-{*trans*-4-[3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (200 mg, 0.48 mmol) was coupled with *p*-formaldehyde (72 mg, 2.4 mmol) following the procedure described in Example 17, except CH_2Cl_2 (5 mL) was added. Also, additional $NaBH(OAc)_3$ was added at intervals to drive the reaction to completion. Formation of the HCl salt gave 6-{*trans*-4-[methyl-3-(4-trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (175 mg, 77%), as a white solid: mp 227-234°C; IR (KBr): 2945, 1771, 1497 cm^{-1} ; 1H NMR (500 MHz, DMSO- d_6): δ 11.48 (s, 1H), 10.00 (br s, 1H), 7.68 (d, J = 8 Hz, 2H), 7.50 (d, J = 8 Hz, 2H), 7.16 (s, 1H), 6.99 (s, 2H), 3.33-3.29 (m, 1H), 3.22-3.14 (m, 1H), 3.08-3.00 (m, 1H), 2.81-2.72 (m, 2H), 2.71 (d, J = 5 Hz, 3H), 2.59-2.51 (m, 1H), 2.15-2.05 (m, 4H), 1.94-1.88 (m, 2H), 1.68-1.51 (m, 4H); CI-MS (methane) (m/z): 433 [M + H] $^+$; calcd for $C_{24}H_{27}F_3N_2O_2$, 433.2103; found, 433.2105; HPLC: method C, 14.09 minutes (95.8%); method D, 20 15.99 minutes (97.3%); Anal. Calcd for $C_{24}H_{27}F_3N_2O_2 \cdot HCl \cdot H_2O$: C, 59.20; H, 6.21; N, 5.75. Found: C, 59.22; H, 6.22; N, 5.55.

EXAMPLE 24

(a) 6-{*trans*-4-[3-(2,4-Difluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one

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(b) 6-(*trans*-4-{[3-(2,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



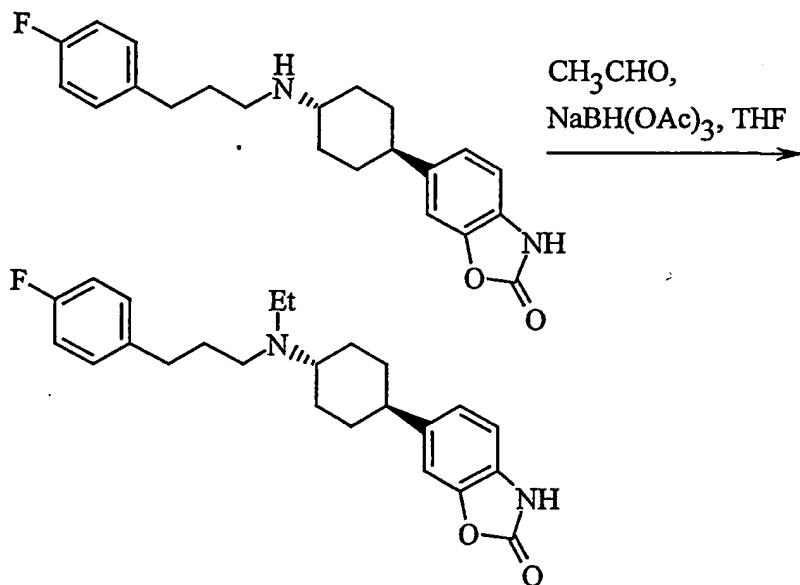
Coupling of ketone 5 and 3-(2,4-difluorophenyl)-1-propylamine, using the method given in Example 1, gave (a) 6-{*trans*-4-[3-(2,4-difluorophenyl)-propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one and (0.75 g, 37%), isolated as the HCl salt: ^1H NMR (500 MHz, DMSO- d_6): δ 11.49 (s, 1H), 8.84 (br s, 2H), 7.40 (ddd, $J = 9, 9, 7$ Hz, 1H), 7.22-7.18 (m, 2H), 7.05 (ddd, $J = 8, 8, 2$ Hz, 1H), 7.01 (dd, $J = 8, 1$ Hz, 1H), 6.99 (d, $J = 8$ Hz, 1H), 3.11-3.02 (m, 1H), 2.98-2.92 (m, 2H), 2.70 (t, $J = 8$ Hz, 2H), 2.56-2.49 (m, 1H), 2.18-2.11 (m, 2H), 1.96-1.86 (m, 4H), 1.51 (m, 4H), and
 (b) 6-{*trans*-4-[3-(2,4-Difluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one and (435 mg, 1.0 mmol) was coupled with *p*-formaldehyde (150 mg, 5.1 mmol) following the procedure described in Example 17, except
 15 CH_2Cl_2 (15 mL) was added. Also, additional $\text{NaBH}(\text{OAc})_3$ was added at

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intervals to drive the reaction to completion. Formation of the HCl salt gave (b) 6-(*trans*-4-{[3-(2,4-difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (314 mg, 72%), as a white solid: mp 269-272°C; IR (KBr): 2947, 1768 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 10.37 (br s, 1H), 7.41 (ddd, *J* = 8, 8, 7 Hz, 1H), 7.22-7.16 (m, 2H), 7.07-7.04 (m, 1H), 7.00 (s, 2H), 3.32-3.28 (m, 1H), 3.20-3.12 (m, 1H), 3.08-2.99 (m, 1H), 2.72-2.61 (m, 5H), 2.59-2.50 (m, 1H), 2.15-2.07 (m, 2H), 2.04-1.96 (m, 2H), 1.90-1.89 (m, 2H), 1.67-1.51 (m, 4H); ESI-MS (*m/z*): 401 [M + H]⁺; HPLC: method A, 5.96 minutes (>99%); Anal. Calcd for C₂₃H₂₆F₂N₂O₂·HCl: C, 63.23; H, 6.23; N, 6.41. Found: C, 63.03; H, 6.16; N, 6.25.

EXAMPLE 25

6-(*trans*-4-{[Ethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one



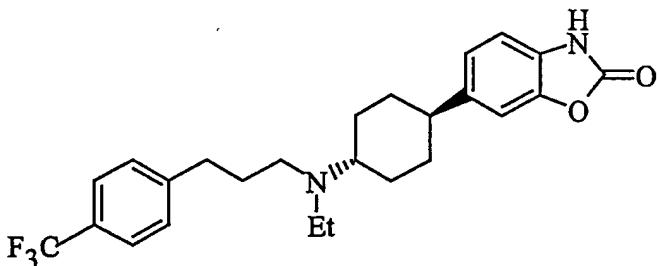
To a stirred solution of 6-{*trans*-4-[3-(4-fluorophenyl)-propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (1.0 g, 2.7 mmol) in THF (60 mL) was added acetaldehyde (240 mg, 5.4 mmol) and 3Å molecular sieves. After stirring the reaction mixture for 5 to 10 minutes, NaBH(OAc)₃ (0.81 mg, 3.8 mmol) was added, and stirring was continued for 0.5 hours. The reaction mixture was concentrated under reduced pressure, and the residue was dissolved in MeOH.

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The solution was brought to pH = 10 with 2N NaOH, filtered through Celite, and concentrated under reduced pressure. Purification by flash chromatography (silica, 89:10:1 CH₂Cl₂:MeOH:NH₄OH), followed by formation of the HCl salt gave 6-
5 (*trans*-4-{[ethyl-[3-(4-fluorophenyl)propyl]amino}-cyclohexyl)-3*H*-benzoxazol-2-one (395 mg, 33%), as a white solid: mp 228-231°C; IR (KBr): 2946, 1769,
1509 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.47 (s, 1H), 9.65 (br s, 1H),
7.33-7.29 (m, 2H), 7.17-7.12 (m, 3H), 7.00 (s, 2H), 3.39-3.32 (m, 1H), 3.24-
3.08 (m, 3H), 3.05-2.98 (m, 1H), 2.68 (q, *J* = 7, 3 Hz, 2H), 2.60-2.50 (m, 1H),
2.14-2.09 (m, 2H), 2.04-1.98 (m, 2H), 1.93-1.87 (m, 2H), 1.69-1.55 (m, 4H),
10 1.26 (t, *J* = 7 Hz, 3H); CI-MS (methane) (*m/z*): 397 [M + H]⁺; HPLC: method A,
6.37 minutes (97.7%); Anal. Calcd for C₂₄H₂₉FN₂O₂·HCl: C, 66.58; H, 6.98; N,
6.47. Found: C, 66.37; H, 7.08; N, 6.25.

EXAMPLE 26

15 6-(*trans*-4-{[Ethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-
2-one



Coupling of 6-{*trans*-4-[3-(4-trifluoromethylphenyl)propylamino]-
20 cyclohexyl}-3*H*-benzoxazol-2-one (200 mg, 0.48 mmol) and acetaldehyde
(42 mg, 0.96 mmol) following the procedure described in Example 24, followed
by formation of the HCl salt, gave 6-(*trans*-4-{[ethyl-[3-(4-fluorophenyl)-
propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one (80 mg, 35%), as an off-white
solid: mp 248-252°C; IR (KBr): 2946, 1771, 1497, 1451 cm⁻¹; ¹H NMR
(500 MHz, DMSO-*d*₆): δ 11.49 (s, 1H), 9.81 (br s, 1H), 7.68 (d, *J* = 8 Hz, 2H),
7.51 (d, *J* = 8 Hz, 2H), 7.16 (s, 1H), 7.00 (s, 1H), 3.40-3.31 (m, 1H), 3.27-3.09 (m,
25 3H), 3.09-2.99 (m, 1H), 2.77 (q, *J* = 7,3 Hz, 2H), 2.59-2.50 (m, 1H), 2.15-2.00 (m,
4H), 1.92-1.88 (m, 2H), 1.69-1.54 (m, 4H), 1.27 (t, *J* = 7 Hz, 3H); CI-MS

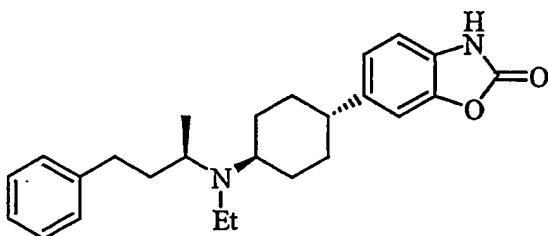
-58-

(methane) (*m/z*): 447 [M + H]⁺; calcd for C₂₅H₂₉F₃N₂O₂, 447.2259; found, 447.2267; HPLC: method C, 14.40 minutes (98.3%); method D, 16.11 minutes (98.5%); Anal. Calcd for C₂₅H₂₉F₃N₂O₂·HCl·0.25H₂O: C, 61.60; H, 6.31; N, 5.75. Found: C, 61.59; H, 6.22; N, 5.58.

5

EXAMPLE 27

6-(*trans*-4-{Ethyl-[(*R*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one

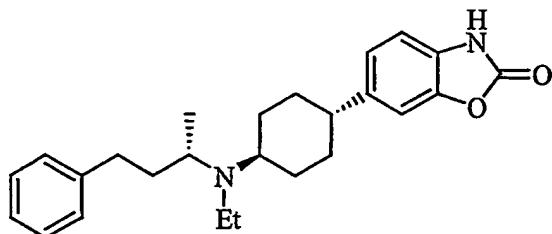


Coupling of 6-{*trans*-4-[(*R*)-1-methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one (370 mg, 1.01 mmol) and acetaldehyde (44 mg, 1.01 mmol) following the procedure described in Example 24, followed by formation of the HCl salt, gave 6-(*trans*-4-{ethyl-[(*R*)-1-methyl-3-phenylpropyl]amino}-cyclohexyl)-3*H*-benzoxazol-2-one (70 mg, 25%), as a pale yellow solid (a mixture of diastereomers): mp 139-158°C; IR (KBr): 2941, 1772, 1497, 1451 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.52 (s, 2H), 9.11 (s, 2H), 7.35-7.21 (m, 10H), 7.18 (m, 4H), 7.00 (s, 2H), 3.20 (m, 2H), 2.81 (m, 2H), 2.54 (m, 2H), 2.20-1.51 (m, 28H), 1.44 (d, *J* = 7 Hz, 3H), 1.32 (d, *J* = 7 Hz, 3H), 1.26 (m, 6H); API-MS (methane) (*m/z*): 393 [M + H]⁺; calcd for C₂₅H₃₂N₂O₂, 393.2542; found, 393.2540; HPLC: method C, 5.77 minutes (97.4%), method D, 11.47 minutes and 11.57 minutes (98.1%); Anal. Calcd for C₂₅H₃₂N₂O₂·HCl·0.5H₂O: C, 68.55; H, 7.82; N, 6.40. Found: C, 68.67; H, 8.03; N, 6.27.

EXAMPLE 28

6-(*trans*-4-{Ethyl-[(*S*)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one

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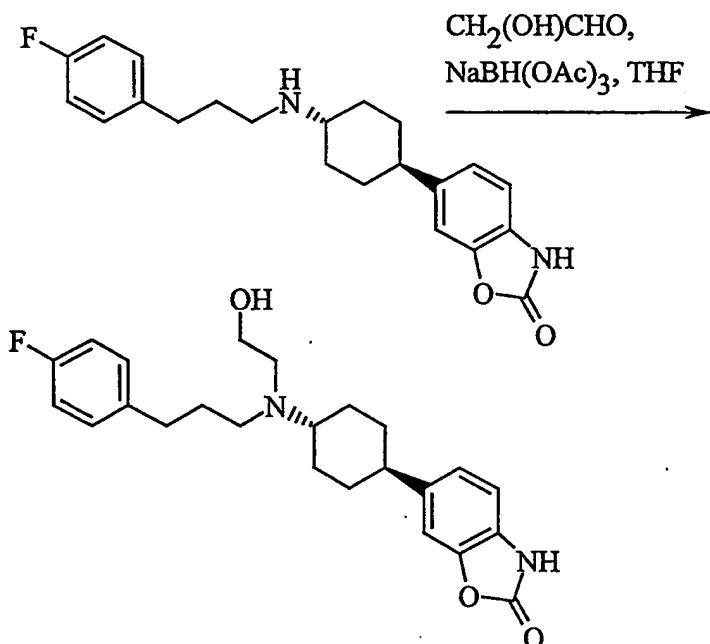
Coupling of 6-{*trans*-4-[{(S)-1-methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one (196 mg, 0.538 mmol) and acetaldehyde (24 mg, 0.538 mmol) following the procedure described in Example 24, followed by formation of the HCl salt, gave 6-(*trans*-4-{ethyl-[{(S)-1-methyl-3-phenylpropyl}amino]cyclohexyl)-3*H*-benzoxazol-2-one (110 mg, 50%), as a pale yellow solid (a mixture of diastereomers): mp 221-246°C; IR (KBr): 3424, 2929, 1771, 1495 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.52 (s, 2H), 9.11 (s, 2H), 7.35-7.21 (m, 10H), 7.18 (m, 4H), 7.00 (s, 2H), 3.20 (m, 2H), 2.81 (m, 2H), 2.54 (m, 2H), 2.20-1.51 (m, 28H), 1.44 (d, *J* = 7 Hz, 3H), 1.32 (d, *J* = 7 Hz, 3H), 1.26 (m, 6H); API-MS (methane) (*m/z*): 393 [M + H]⁺; HPLC: method C, 5.88 minutes (97.4%), method D, 11.32 minutes (>99%); Anal. Calcd for C₂₅H₃₂N₂O₂·HCl·H₂O: C, 67.17; H, 7.89; N, 6.27. Found: C, 67.18; H, 7.69; N, 5.98.

15

EXAMPLE 29

6-{*trans*-4-[[3-(4-Fluorophenyl)propyl]-2-hydroxyethyl]amino]cyclohexyl}-3*H*-benzoxazol-2-one

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To a stirred solution of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (0.5 g, 1.2 mmol) in THF (25 mL) and CH₂Cl₂ (5 mL) was added Et₃N (0.17 mL, 1.2 mmol), glycoaldehyde (110 mg,

5 1.8 mmol), and 3 Å molecular sieves. After stirring the reaction mixture for 5 to 10 minutes, NaBH(OAc)₃ was added, and stirring was continued for 0.5 hours.

The reaction mixture was concentrated under reduced pressure, and the residue 10 was dissolved in MeOH. The solution was brought to pH = 11 with 2N NaOH, filtered through Celite, and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:9.5:0.5 CH₂Cl₂:MeOH:NH₄OH) and (silica, 90:10 CH₂Cl₂:MeOH) resulted in isolation of the free base (120 mg, 24%).

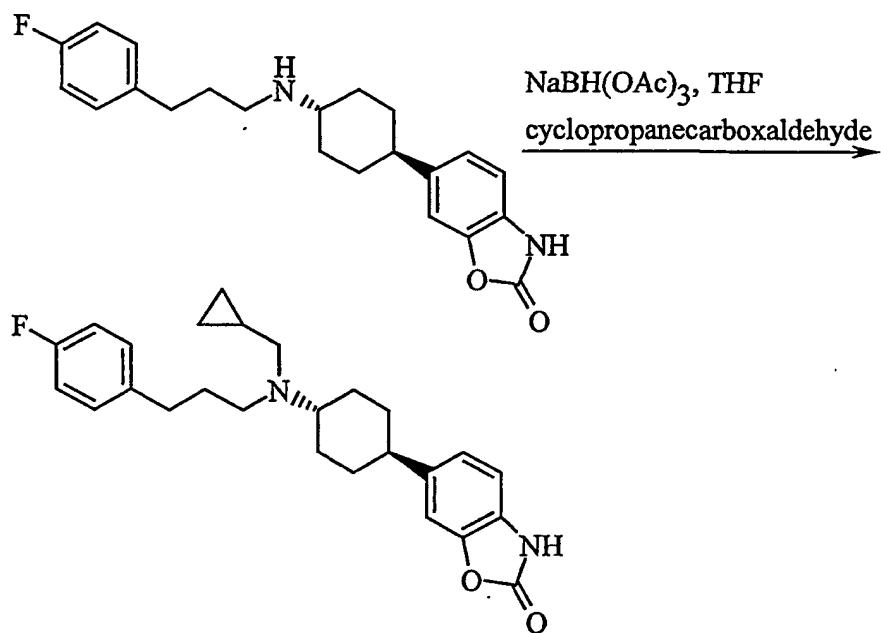
Formation of the HCl salt gave compound 6-{*trans*-4-[[(3-(4-fluorophenyl)-propyl)-(2-hydroxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one as a white solid: mp 259-262°C; IR (KBr): 3314, 2949, 1765, 1509 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 9.40 (br s, 1H), 7.32-7.28 (m, 2H), 7.18-15 7.12 (m, 3H), 7.00 (s, 2H), 5.34-5.31 (m, 1H), 3.76-3.74 (m, 2H), 3.49-3.39 (m, 1H), 3.21-3.08 (m, 3H), 2.65 (t, *J* = 8 Hz, 2H), 2.60-2.49 (m, 2H), 2.18-1.99 (m, 4H), 1.98-1.86 (m, 2H), 1.71-1.52 (m, 4H); API-MS (methane) (*m/z*): 413 [M+H]⁺; calcd for C₂₄H₂₉FN₂O₃, 413.2240; found, 413.2239; HPLC: method A,

-61-

5.47 minutes (98.9%); method B, 11.11 minutes (98.5%); Anal. Calcd for C₂₄H₂₉FN₂O₃·HCl·0.5H₂O: C, 62.94; H, 6.82; N, 6.12. Found: C, 63.10; H, 6.67; N, 6.06.

EXAMPLE 30

- 5 6-(*trans*-4-{Cyclopropylmethyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one



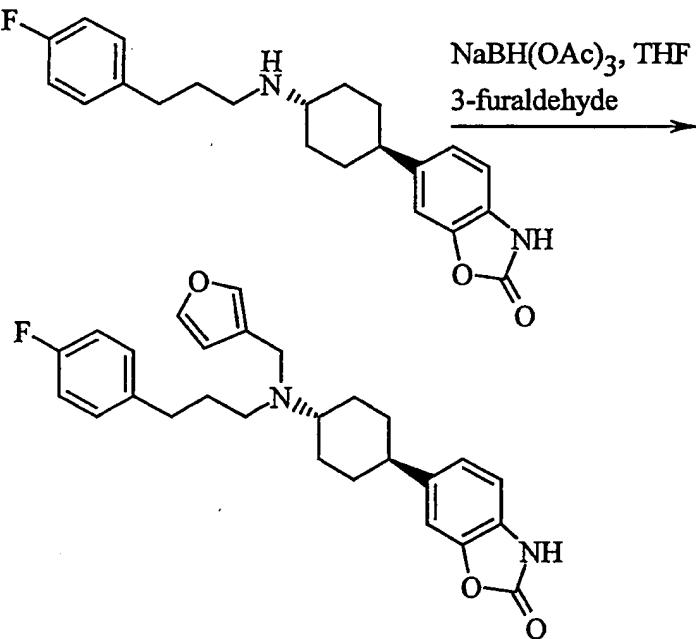
The free base of 6-(*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (400 mg, 0.99 mmol) was made by the addition of 1N NaOH (0.99 mL, 0.99 mmol) to 6-(*trans*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl)-3*H*-benzoxazol-2-one hydrochloride in THF (25 mL) and MeOH (10 mL). Cyclopropanecarboxaldehyde (70 mg, 0.99 mmol) was added, followed by NaBH(OAc)₃ (300 mg, 1.4 mmol). Additional NaBH(OAc)₃ and cyclopropanecarboxaldehyde were added at intervals, over 28 hours, to drive the reaction to completion. The solution was brought to pH = 11 with solid NaOH and then concentrated under reduced pressure. Purification by flash chromatography (silica, 90:9.5:0.5 CH₂Cl₂:MeOH:NH₄OH) followed by formation of the HCl salt gave 6-(*trans*-4-{cyclopropylmethyl-[3-(4-fluorophenyl)propyl]amino}-cyclohexyl)-3*H*-benzoxazol-2-one (347 mg, 76%), as a white solid: mp 221-

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225°C; IR (KBr): 2937, 1764, 1510 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 11.50 (s, 1H), 9.78 (br s, 1H), 7.33-7.29 (m, 2H), 7.18-7.12 (m, 3H), 7.02 (s, 2H), 3.50-3.42 (m, 1H), 3.24-2.97 (m, 4H), 2.72-2.61 (m, 2H), 2.59-2.55 (m, 1H), 2.18-2.01 (m, 4H), 1.94-1.88 (m, 2H), 1.69-1.53 (m, 4H), 1.18-1.09 (m, 1H), 0.68-0.59 (m, 2H), 0.46-0.36 (m, 2H); ESI-MS (m/z): 423 [M + H]⁺; HPLC: method A, 6.22 minutes (98.5%); Anal. Calcd for C₂₆H₃₁FN₂O₂·HCl: C, 68.04; H, 7.03; N, 6.10. Found: C, 67.65; H, 7.07; N, 5.95.

EXAMPLE 31

10 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]furan-3-ylmethylamino}cyclohexyl)-3*H*-benzoxazol-2-one



The free base of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one was made by the addition of K₂CO₃ (170 mg, 1.2 mmol) to 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one hydrochloride (500 mg, 1.2 mmol) in THF (50 mL). To this suspension was added 3-furaldehyde (470 mg, 4.9 mmol) and, after 10 minutes, NaBH(OAc)₃ (520 mg, 2.4 mmol) was added. After stirring the reaction mixture 3 hours, additional NaBH(OAc)₃ (520 mg, 2.4 mmol) was added, and stirring continued for 14.5 hours. The solution was diluted with MeOH and brought to pH = 13 with

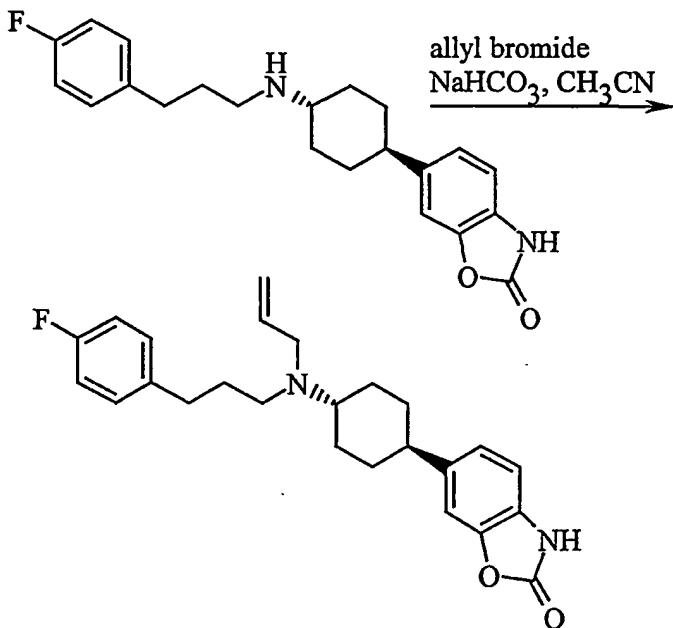
-63-

solid NaOH. The solution was then concentrated under reduced pressure.

Purification by flash chromatography (silica, 90:9.5:0.5 CH₂Cl₂:MeOH:NH₄OH), followed by formation of the HCl salt, gave 6-(*trans*-4-{[3-(4-fluorophenyl)-propyl]furan-3-ylmethylamino}cyclohexyl)-3*H*-benzoxazol-2-one (272 mg, 46%) as an off-white solid: mp 225-227°C; IR (KBr): 2929, 1773, 1510 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.49 (s, 1H), 9.99 (br s, 1H), 7.90 (s, 1H), 7.76 (s, 1H), 7.27-7.24 (m, 2H), 7.18 (s, 1H), 7.14-7.10 (m, 2H), 7.02-6.98 (m, 2H), 6.75 (s, 1H), 4.30-4.18 (m, 2H), 3.33-3.29 (m, 1H), 3.20-3.12 (m, 1H), 3.01-2.93 (m, 1H), 2.67-2.53 (m, 3H), 2.22-2.15 (m, 2H), 2.07-1.88 (m, 4H), 1.78-1.66 (m, 2H), 1.62-1.49 (m, 2H); ESI-MS (*m/z*): 449 [M + H]⁺; HPLC: method A, 6.27 minutes (99.8%); Anal. Calcd for C₂₇H₂₉FN₂O₃·HCl: C, 66.87; H, 6.23; N, 5.78. Found: C, 66.54; H, 6.27; N, 5.48.

EXAMPLE 32

15 6-(*trans*-4-{Allyl-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one



To a stirred suspension of 6-(*trans*-4-[3-(4-fluorophenyl)-propylamino]-cyclohexyl)-3*H*-benzoxazol-2-one (400 mg, 0.99 mmol) in THF (40 mL) and DMF (3 mL) was added NaHCO₃ (180 mg, 2.2 mmol) and allyl bromide

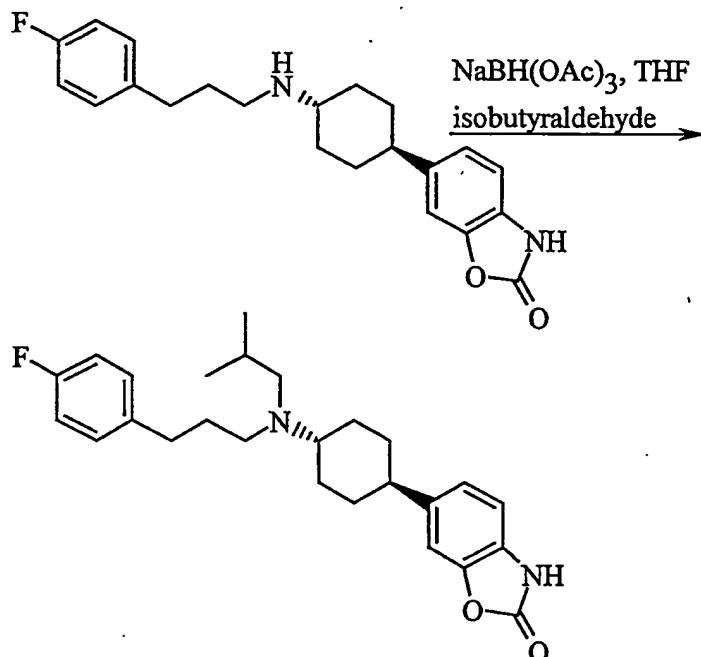
-64-

(130 mg, 1.1 mmol). After refluxing overnight, additional DMF (1.5 mL), allyl bromide (30 mg, 29 mmol), and NaHCO₃ (21 mg, 0.25 mmol) were added. The reaction mixture was refluxed for 12 hours and then cooled to room temperature. The material was diluted with water and extracted with EtOAc (3X). The combined organics were washed with water, saturated NaCl solution (3X), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:10 CH₂Cl₂:MeOH), followed by formation of the HCl salt, gave 6-(*trans*-4-{allyl-[3-(4-fluorophenyl)propyl]-amino}cyclohexyl)-3*H*-benzoxazol-2-one (138 mg, 31%), as a white solid: mp 224-230°C; IR (KBr): 10 2943, 1770, 1510 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.51 (s, 1H), 10.38 (br s, 1H), 7.31-7.28 (m, 2H), 7.17-7.11 (m, 3H), 7.00 (s, 2H), 6.11-6.04 (m, 1H), 5.55 (d, *J* = 17 Hz, 1H), 5.45 (d, *J* = 10 Hz, 1H), 3.87-3.71 (m, 2H), 3.38-3.31 (m, 1H), 3.19-3.13 (m, 1H), 3.05-2.92 (m, 1H), 2.70-2.51 (m, 3H), 2.18-2.12 (m, 2H), 2.07-1.99 (m, 2H), 1.92-1.87 (m, 2H), 1.72-1.50 (m, 4H); (ESI-MS (*m/z*): 409 [M + H]⁺; HPLC: method B, 11.34 minutes (98.1%); Anal. Calcd for C₂₅H₂₉FN₂O₂·HCl: C, 67.48; H, 6.80; N, 6.30. Found: C, 67.29; H, 6.93; N, 6.07.

EXAMPLE 33

6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]isobutylamino}cyclohexyl)-3*H*-benzoxazol-2-one

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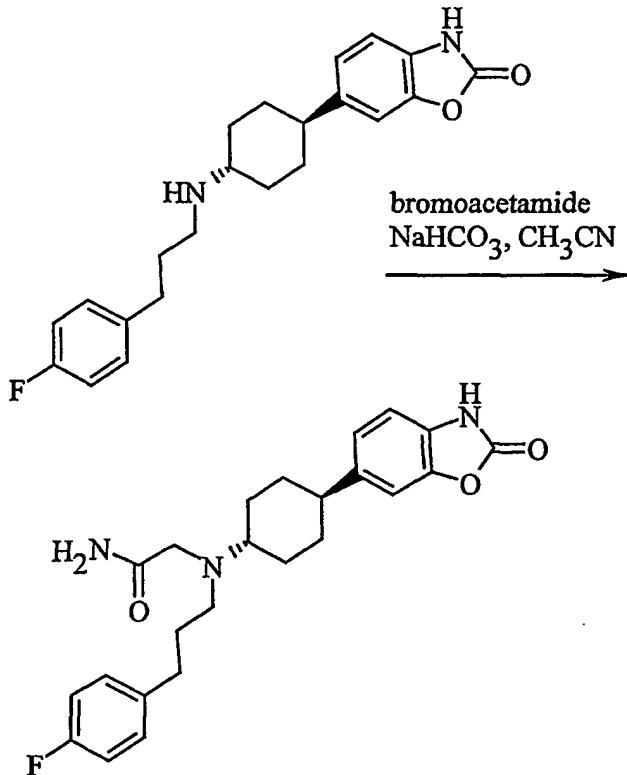
The free base of 6-{*trans*-4-[3-(4-fluorophenyl)-propylamino]cyclohexyl}-3*H*-benzoxazol-2-one was made by the addition of K₂CO₃ (140 mg, 1.0 mmol) to 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one hydrochloride (400 mg, 1.0 mmol) in THF (40 mL). The solution was warmed to dissolve the free base and then cooled to room temperature. Isobutyraldehyde (280 mg, 4.0 mmol) was added, followed by NaBH(OAc)₃ (420 mg, 2.0 mmol) after 10 minutes. The reaction mixture was stirred for 2.5 days and then concentrated under reduced pressure. The solution was diluted with MeOH and brought to pH = 10 with solid NaOH. The solution was then concentrated under reduced pressure. Purification by flash chromatography (silica, 95:4.75:0.25 CH₂Cl₂:MeOH:NH₄OH), followed by formation of the HCl salt, gave 6-(*trans*-4-{[3-(4-fluorophenyl)propyl]-isobutylamino}cyclohexyl)-3*H*-benzoxazol-2-one (327 mg, 46%), as a white solid: mp 199-201°C; IR (KBr): 2941, 1769, 1510 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 11.51 (s, 1H), 9.16 (br s, 1H), 7.32-7.29 (m, 2H), 7.17-7.12 (m, 3H), 6.99 (s, 2H), 3.38-3.33 (m, 1H), 3.13-3.03 (m, 3H), 2.86-2.80 (m, 1H), 2.66-2.62 (m, 2H), 2.58-2.51 (m, 1H), 2.13-1.97 (m, 5H), 1.92-1.87 (m, 2H), 1.74-1.56 (m, 4H), 1.02-0.98 (m, 6H); ESI-MS (m/z): 425 [M + H]⁺; HPLC: method A, 6.38 minutes (98.7%); Anal. Calcd for

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$C_{26}H_{33}FN_2O_2\cdot HCl$: C, 67.74; H, 7.43; N, 6.08. Found: C, 67.65; H, 7.29; N, 5.93.

EXAMPLE 34

2-{{[3-(4-Fluorophenyl)propyl]amino}-[4-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-
5 cyclohexyl]amino}acetamide



To a stirred suspension of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (110 mg, 0.81 mmol) in DMF (15 mL) was added $NaHCO_3$ (140 mg, 1.6 mmol) and bromoacetamide (300 mg, 0.74 mmol).

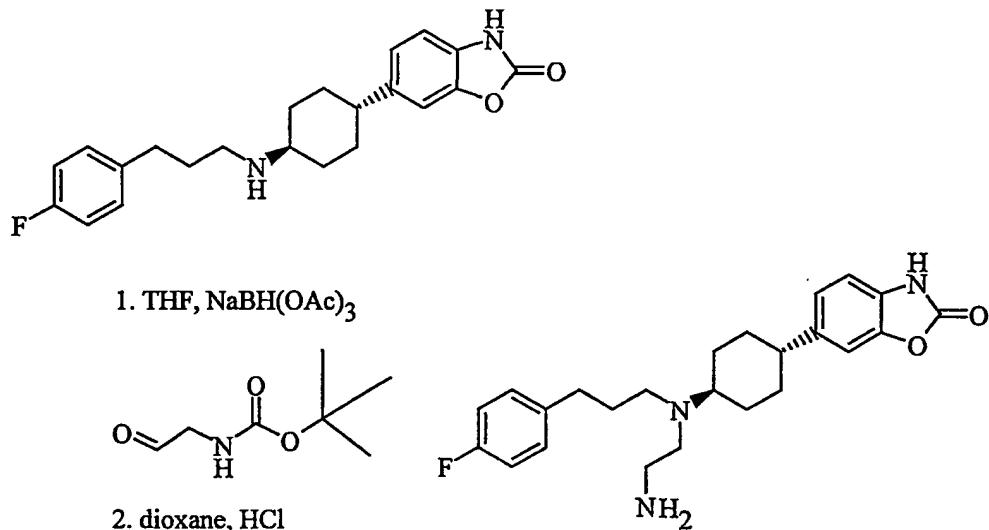
10 After 16 hours the reaction mixture was warmed to 50°C. After 4 hours, additional bromide (150 mg, 0.37 mmol) and $NaHCO_3$ (31 mg, 0.37 mmol) were added, and the temperature was increased to 75°C. After 4 hours, the reaction mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The combined organics were washed with water, saturated $NaCl$, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:4.75:0.25 CH_2Cl_2 :MeOH:NH₄OH) followed by

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conversion to the HCl salt gave compound 2-{{[3-(4-fluorophenyl)propyl]-[4-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-cyclohexyl]amino}acetamide (60 mg, 17%), as a white solid: mp 266-270°C; IR (KBr): 3331, 3149, 2943, 1762, 1691 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.47 (s, 1H), 9.08 (br s, 1H), 7.96 (br s, 1H), 7.73 (br s, 1H), 7.29-7.25 (m, 2H), 7.17-7.01 (m, 3H), 6.99 (s, 2H), 4.05-4.02 (m, 1H), 3.81-3.78 (m, 1H), 3.47-3.38 (m, 1H), 3.22-3.12 (m, 3H), 2.63 (t, *J* = 8 Hz, 2H), 2.57-2.52 (m, 1H), 2.14-1.87 (m, 6H), 1.71-1.49 (m, 4H); ESI-MS (*m/z*): 426 [M + H]⁺; HPLC: method A, 5.44 minutes (98.0%); HPLC: method E, 6.50 minutes (>99%); Anal. Calcd for C₂₄H₂₈FN₃O₃·HCl: C, 61.80; H, 6.37; N, 9.01. Found: C, 61.78; H, 6.27; N, 8.80.

EXAMPLE 35

6-(*trans*-4-{{(2-Aminoethyl)-[3-(4-fluorophenyl)propyl]amino}cyclohexyl}-3*H*-benzoxazol-2-one



To a stirred solution of 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (HCl salt) (0.5 g, 1.2 mmol) in THF (25 mL) was added Et₃N (0.19 mL, 1.4 mmol), *tert*-butyl N-(2-oxoethyl)carbamate (220 mg, 1.9 mmol) and 3 Å molecular sieves. After stirring the reaction mixture for 10 minutes, NaBH(OAc)₃ (0.43 g, 0.39 mmol) was added, and stirring was continued for 5.75 hours. The reaction mixture was diluted with MeOH, brought to pH = 8 with 1N NaOH, filtered, and concentrated under reduced pressure.

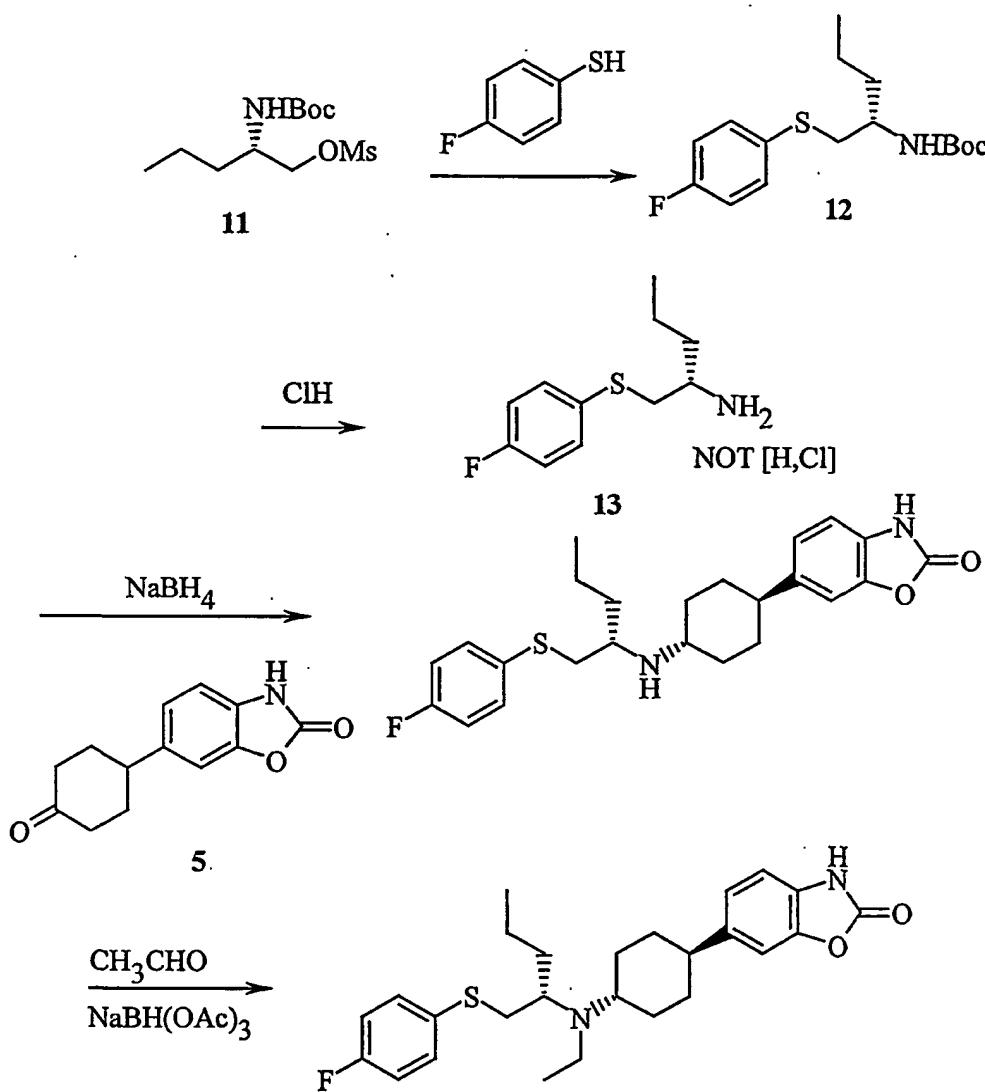
-68-

Purification by flash chromatography (silica, 95:5 CH₂Cl₂:MeOH) gave 220 mg of Boc protected amine. The residue was dissolved in dioxane (12 mL), and 4 M HCl in dioxane (2 mL) was added. The mixture was stirred for 2 hours, concentrated under reduced pressure, and purified by flash chromatography (silica, 89:10:1 CH₂Cl₂:MeOH:NH₄OH). Formation of the HCl salt gave 5 (silica, 89:10:1 CH₂Cl₂:MeOH:NH₄OH). Formation of the HCl salt gave 6-(*trans*-4-{(2-aminoethyl)-[3-(4-fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one (133 mg, 27%), as a white solid: mp 161-169°C; IR (KBr): 2929, 1764, 1656 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.24-7.22 (m, 2H), 7.10-7.06 (m, 3H), 6.95-6.90 (m, 2H), 3.50-3.10 (br s, 3H), 2.60-2.41 (m, 10H), 10 1.83-1.76 (m, 4H), 1.79-1.63 (m, 2H), 1.49-1.31 (m, 4H); ESI-MS (*m/z*): 412 [M + H]⁺; Anal. Calcd for C₂₄H₃₀FN₃O₂: C, 70.05; H, 7.35; N, 10.21. Found: C, 69.86; H, 7.45; N, 10.07.

EXAMPLE 36

- (a) (*S*)-6-{*trans*-4-[1-(4-Fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-3*H*-benzoxazol-2-one
15
(b) (*S*)-6-{*trans*-4-[Ethyl(1-(4-fluorophenylsulfanyl)pentan-2-yl)amino]-cyclohexyl}-3*H*-benzoxazol-2-one

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Step 1: To a stirred solution of mesylate 11 (2.23 g, 7.95 mmol) and 4-fluorobenzenethiol (1.02 g, 7.95 mmol) in THF/2-PrOH (30 mL, 1:1) was added sodium borohydride (0.39 g, 10.34 mmol). The reaction mixture was stirred overnight then diluted with EtOAc (100 mL) and washed successively with 20% KOH (3×30 mL), water (30 mL), and saturated NaCl (30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure.

5

Purification by flash chromatography (silica, 7:1 Hexanes/EtOAc) gave Boc-protected amine 12 (1.24 g, 50%), as a white solid: ^1H NMR (500 MHz, CDCl_3):

10

δ 7.38 (dd, $J = 7, 4$ Hz, 2H), 6.98 (t, $J = 4$ Hz, 2H), 4.51 (br s, 1H), 3.84 (br s, 1H), 3.01 (m, 2H), 1.57 (m, 2H), 1.54 (s, 9H), 1.37 (m, 2H), 0.89 (t, $J = 4$ Hz, 3H).

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Step 2: To a stirred solution of Boc-amine 12 (1.24 g, 3.96 mmol) in dioxane (5 mL) was added HCl in dioxane (1.48 mL of a 4M solution, 5.92 mmol). The reaction mixture was concentrated under reduced pressure after 1 hour to give amine 13 (0.93 g, 94%), as a white solid: ^1H NMR (500 MHz, CDCl₃): δ 8.65 (br s, 2H), 7.55 (dd, J = 7, 4 Hz, 2H), 6.99 (t, J = 4 Hz, 2H), 3.29-3.13 (m, 3H), 1.84 (m, 2H), 1.38 (m, 2H), 0.88 (t, J = 4 Hz, 3H).

Step 3: To a stirred solution of amine 13 (0.93 g, 3.72 mmol) in 2-PrOH (30 mL) was added 4Å molecular sieves and ketone 5 (0.88 g, 3.72 mmol). The reaction mixture was stirred for 3 hours. Sodium borohydride (0.19 g, 5.21 mmol) was added, and the mixture was stirred overnight. The reaction mixture was filtered and concentrated under reduced pressure. Purification by flash chromatography (silica, 1.5:1 Hexanes/EtOAc) gave (a) (S)-6-{*trans*-4-[1-(4-fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-3*H*-benzoxazol-2-one (282 mg, 17%), as a white solid: ^1H NMR (300 MHz, CDCl₃): δ 7.40 (m, 2H), 7.01-6.93 (m, 5H), 3.07-2.81 (m, 3H), 2.47 (m, 2H), 1.93-1.71 (m, 4H), 1.57-1.14 (m, 8H), 0.87 (t, J = 6 Hz, 3H).

Step 4: To (a) (S)-6-{*trans*-4-[1-(4-fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-3*H*-benzoxazol-2-one (292 mg, 0.687 mmol) in THF (10 mL) was added acetaldehyde (30 mg, 0.68 mmol) and 4Å molecular sieves. After stirring for 0.25 hours, sodium triacetoxyborohydride (204 mg, 0.962 mmol) was added. The reaction mixture was stirred for 0.75 hours then concentrated under reduced pressure. The crude residue was taken up in methanol (10 mL), and solid NaOH was added until the pH was >8. The solution was concentrated under reduced pressure. Purification by flash chromatography (silica, 1:1 Hexanes:EtOAc) gave (b) (S)-6-{*trans*-4-[ethyl(1-(4-fluorophenylsulfanyl)pentan-2-yl)amino]cyclohexyl}-3*H*-benzoxazol-2-one (210 mg, 67%), as a clear oil: IR (KBr): 3219, 2926, 1764, 1589 cm⁻¹; ^1H NMR (500 MHz, CDCl₃): δ 7.34 (m, 2H), 7.05-6.92 (m, 5H), 3.02 (m, 3H), 2.79 (m, 1H), 2.64 (m, 6H), 2.38 (m, 1H), 1.93-1.78 (m, 4H), 1.47-1.29 (m, 4H), 0.93 (t, J = 5 Hz, 3H), 0.89 (t, J = 6 Hz, 3H); API-MS (*m/z*): 457 [M + H]⁺; calcd for C₂₆H₃₃FN₂O₂S,

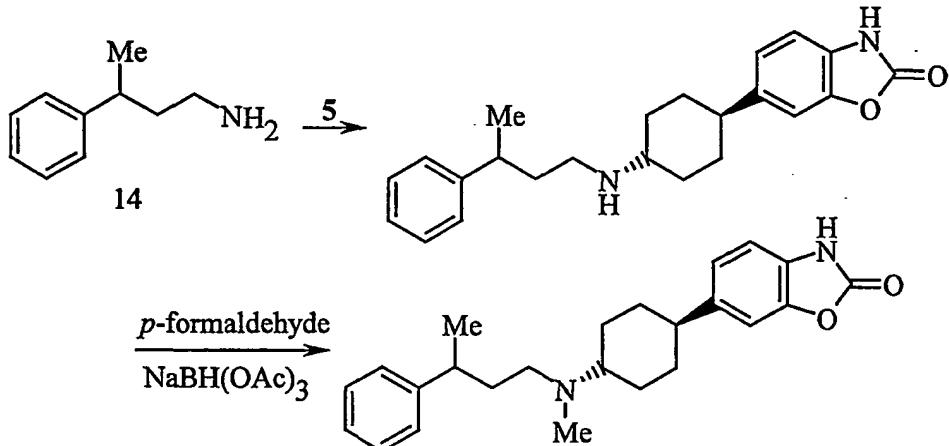
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457.2325; found, 457.2324; HPLC: method C, 6.55 minutes (>99%), method D, 12.37 minutes (>99%).

EXAMPLE 37

(a) 6-[*trans*-4-(3-Phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one

5 (b) 6-[*trans*-4-(Methyl-3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one



Step 1: To a stirred solution of amine 14 (1.3 g, 6.2 mmol) in THF (75 mL) was added 5 (1.44 g, 6.22 mmol). The reaction mixture was stirred for 1 hour, NaBH₄ (329 mg, 8.71 mmol) was added followed by water (30 mL). The reaction mixture was stirred for 45 minutes then diluted with EtOAc. The mixture was washed with 1N HCl and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:5:1 CH₂Cl₂:MeOH:NH₄OH) gave 6-[*trans*-4-(3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one (640 mg, 28%), as a white solid: ¹H NMR (300 MHz, DMSO-d₆): δ 7.31-7.11 (m, 7H), 6.94 (s, 1H), 2.78 (m, 1H), 2.45-2.35 (m, 5H), 1.87 (br d, *J* = 10 Hz, 2H), 1.73 (br d, *J* = 10 Hz, 2H), 1.68 (m, 2H), 1.44 (dd, *J* = 10, 10, 10, 2 Hz, 2H), 1.19 (d, *J* = 4 Hz, 3H), 1.08 (dd, *J* = 10, 10, 10, 2 Hz, 2H).

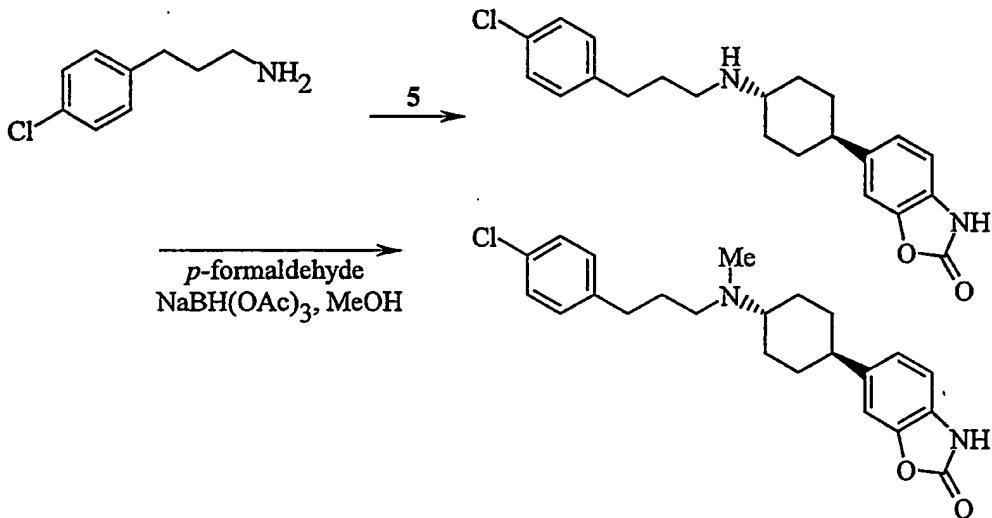
Step 2: To a stirred solution of 6-[*trans*-4-(3-phenylbutylamino)-cyclohexyl]-3*H*-benzoxazol-2-one (638 mg, 1.75 mmol) in MeOH (10 mL) containing water (0.5 mL) was added *p*-formaldehyde (263 mg, 8.76 mmol). The reaction mixture was stirred for 2 hours, and NaBH₄ (519 mg, 2.45 mmol) was added. The reaction mixture was stirred for 3 hours. The reaction was treated with

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solid NaOH until a clear solution resulted and concentrated under reduced pressure. Purification by flash chromatography (95:5:1 CH₂Cl₂:MeOH:NH₄OH) gave 6-[*trans*-4-(methyl-3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one (231 mg, 35%), as a white solid: mp 61-70°C; IR (KBr): 2928, 1774 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.29-7.12 (m, 7H), 6.97 (s, 1H), 2.76 (m, 1H), 2.49-2.26 (m, 5H), 2.14 (s, 3H), 1.77 (m, 4H), 1.67 (m, 2H), 1.43 (m, 2H), 1.27 (m, 2H), 1.17 (d, J = 4 Hz, 3H); API-MS (*m/z*): 379 [M + H]⁺; HPLC: method A, 5.99 minutes (94.3%); HPLC: method B, 10.97 minutes (>99%); Anal. Calcd for C₂₄H₃₀N₂O₂·0.5H₂O: C, 74.39; H, 8.06; N, 7.23. Found: C, 74.41; H, 7.90; N, 7.31.

EXAMPLE 38

- (a) 6-{*trans*-4-[3-(4-Chlorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one
 (b) 6-(*trans*-4-{[3-(4-Chlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



Step 1: To a solution of 3-(4-chlorophenyl)-1-propylamine hydrochloride (1.5 g, 7.3 mmol) in 2-propanol (50 mL) was added Et₃N (1.1 mL, 8.0 mmol),
 20 ketone 5 (1.7 g, 7.3 mmol), THF (25 mL), and 3Å molecular sieves. The reaction mixture was warmed to dissolve ketone 5 and then stirred at room temperature for 2.25 hours. Sodium borohydride (550 mg, 14.5 mmol) was added, and the reaction

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mixture was stirred for 12 hours. The reaction was quenched with MeOH, and the mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:10 CH₂Cl₂/MeOH) followed by trituration/recrystallization with MeOH gave 6-{*trans*-4-[3-(4-chlorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (683 mg, 24%), as a white solid: ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.32 (d, *J* = 8 Hz, 2H), 7.23 (d, *J* = 8 Hz, 2H), 7.12 (s, 1H), 6.98-6.93 (m, 2H), 2.61 (t, *J* = 7 Hz, 2H), 2.56 (t, *J* = 7 Hz, 2H), 2.48-2.38 (m, 2H), 1.94 (br d, *J* = 10 Hz, 2H), 1.77 (br d, *J* = 10 Hz, 2H), 1.72-1.66 (m, 2H), 1.44 (dddd, *J* = 12, 12, 12, 3 Hz, 2H), 1.12 (dddd, *J* = 12, 12, 12, 3 Hz, 2H).

Step 2: To a stirred solution of 6-{*trans*-4-[3-(4-chlorophenyl)-propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (655 mg, 1.7 mmol) in MeOH (20 mL) and CH₂Cl₂ (25 mL) was added *p*-formaldehyde (0.70 mL of a 37 wt% solution in H₂O, 8.5 mmol). The reaction mixture was warmed to dissolve compound the amine, and then stirred at room temperature for 15 minutes. NaBH(OAc)₃ was added and stirring was continued for 12 hours. The reaction mixture was brought to pH 8 with solid NaOH, concentrated under reduced pressure, and purified by flash chromatography (silica, 95:4.5:0.5 CH₂Cl₂:MeOH:NH₄OH). Formation of the HCl salt, followed by recrystallization (MeOH:Et₂O) gave 6-(*trans*-4-{[3-(4-chlorophenyl)propyl]-methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one (461 mg, 66%), as a white solid: mp 267-271°C; IR (KBr): 2949, 1769, 1494, 1452 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 10.39 (s, 1H), 7.37 (d, *J* = 8 Hz, 2H), 7.30 (d, *J* = 8 Hz, 2H), 7.16 (s, 1H), 7.00 (br s, 2H), 3.33-3.26 (m, 1H), 3.18-3.10 (m, 1H), 3.04-2.95 (m, 1H), 2.69 (d, *J* = 5 Hz, 3H), 2.68-2.62 (m, 2H), 2.58-2.51 (m, 1H), 2.18-1.98 (m, 4H), 1.93-1.87 (m, 2H), 1.69-1.51 (m, 4H); HRMS-APCI (*m/z*): [M + H]⁺ calcd for C₂₃H₂₇ClN₂O₂, 399.1839; found, 399.1831; HPLC: method A, 6.35 minutes (98.6%); method B, 11.82 minutes (99.1%); Anal. Calcd for C₂₃H₂₇ClN₂O₂·HCl·0.25H₂O: C, 62.80; H, 6.53; N, 6.37. Found: C, 62.94; H, 6.57; N, 6.21.

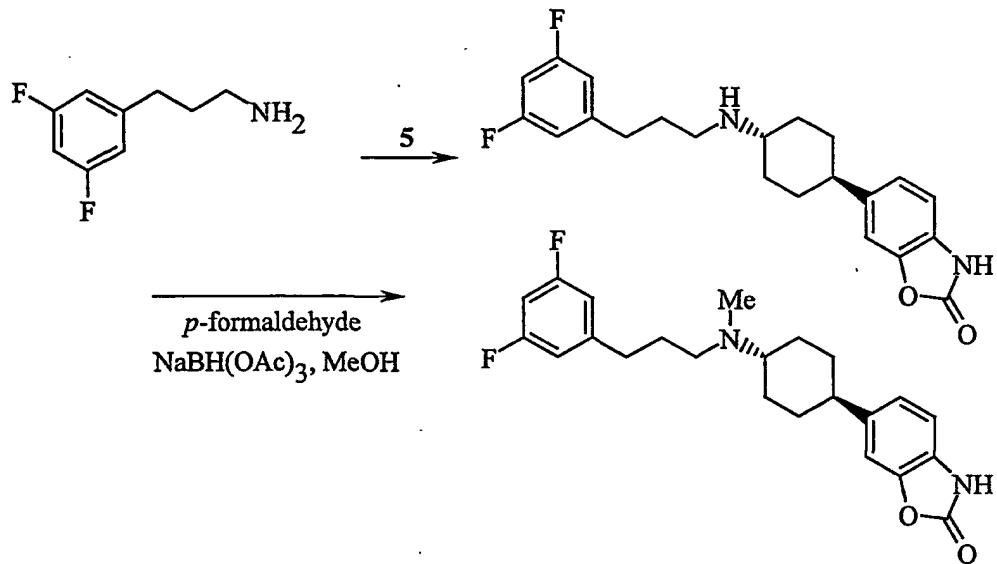
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EXAMPLE 39

(a) 6-(*trans*-4-[3-(3,5-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one

(b) 6-(*trans*-4-{[3-(3,5-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one

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Step 1: Condensation of 3-(3,5-difluorophenyl)-1-propylamine (1.5 g, 6.5 mmol) and ketone 5 (1.5 g, 6.5 mmol), following the procedure described in Example 1, gave 6-(*trans*-4-[3-(3,5-difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (640 mg, 26%), as a white solid: ^1H NMR (500 MHz, DMSO- d_6): δ 7.13 (s, 1H), 7.01-6.92 (m, 5H), 2.66 (t, J = 8 Hz, 2H), 2.57 (t, J = 8 Hz, 2H), 2.49-2.40 (m, 2H), 1.95 (br d, J = 10 Hz, 2H), 1.78 (br d, J = 10 Hz, 2H), 1.74-1.68 (m, 2H), 1.45 (dded, J = 13, 13, 13, 3 Hz, 2H), 1.14 (dded, J = 13, 13, 13, 3 Hz, 2H).

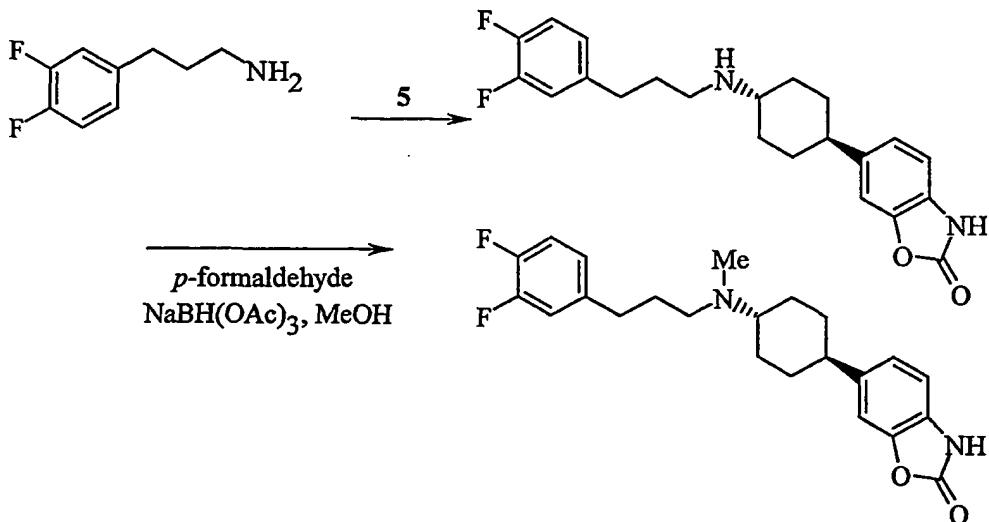
Step 2: Condensation of 6-(*trans*-4-[3-(3,5-difluorophenyl)propylamino]-cyclohexyl)-3*H*-benzoxazol-2-one (600 mg, 1.5 mmol) and *p*-formaldehyde (0.63 mL of a 37 wt% solution in H₂O, 7.8 mmol), following the procedure described in Example 17 followed by conversion to the HCl salt, gave 6-(*trans*-4-{[3-(3,5-difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (465 mg, 71%), as a white solid: mp 270-275°C; IR (KBr): 2950, 1762, 1626, 1596 cm⁻¹; ^1H NMR (500 MHz, DMSO- d_6): δ 11.49 (s, 1H), 10.15 (s, 1H),

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7.17 (s, 1H), 7.09-7.01 (m, 4H), 7.00 (s, 1H), 3.36-3.29 (m, 1H), 3.19-3.10 (m, 1H), 3.05-2.97 (m, 1H), 2.79-2.68 (m, 5H), 2.60-2.53 (m, 1H), 2.18-2.00 (m, 4H), 1.91 (br d, $J = 11$ Hz, 2H), 1.69-1.51 (m, 4H); ESI (m/z): 401 [M + H]⁺; HPLC: method A, 6.42 minutes (98.2%); Anal. Calcd for C₂₃H₂₆F₂N₂O₂·HCl: C, 5 63.23; H, 6.23; N, 6.41. Found: C, 63.04; H, 6.33; N, 6.54.

EXAMPLE 40

- (a) 6-(*trans*-4-[3-(3,4-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one
 10 (b) 6-(*trans*-4-{[3-(3,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



Step 1: Coupling of ketone 5 and 3-(3,4-difluorophenyl)-1-propylamine, using the method given in Example 1, gave 6-(*trans*-4-[3-(3,4-difluorophenyl)-propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (690 mg, 37%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.33-7.24 (m, 2H), 7.12 (d, $J = 1$ Hz, 1H), 7.06-7.02 (m, 1H), 6.98-6.93 (m, 2H), 3.51-3.10 (br s, 2H), 2.62 (dd, $J = 8, 8$ Hz, 2H), 2.55 (dd, $J = 7, 7$ Hz, 2H), 2.48-2.38 (m, 2H), 1.98-1.91 (m, 2H), 1.80-1.73 (m, 2H), 1.71-1.65 (m, 2H), 1.44 (dd, $J = 10, 10, 10, 3$ Hz, 2H), 1.13 (dd, $J = 10, 10, 10, 3$ Hz, 2H).

Step 2: Condensation of 6-(*trans*-4-[3-(3,4-difluorophenyl)propylamino]-cyclohexyl)-3*H*-benzoxazol-2-one (400 mg, 1.0 mmol) with *p*-formaldehyde

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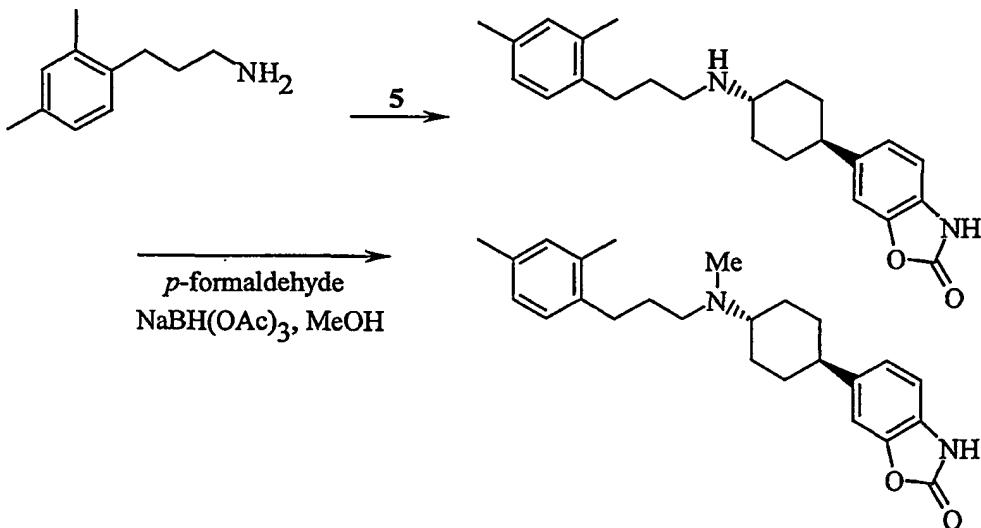
(740 mg, 24.7 mmol) following the procedure described in Example 17, except CH₂Cl₂ (15 mL) was also added, followed by formation of the HCl salt, gave 6-(*trans*-4-{[3-(3,4-difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (226 mg, 52%), as a white solid: mp 224-227°C; IR (KBr):

5 2945, 1764 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 9.94 (s, 1H), 7.40-7.34 (m, 2H), 7.16 (s, 1H), 7.12-7.09 (m, 1H), 7.00 (s, 2H), 3.33-3.29 (m, 1H), 3.18-3.11 (m, 1H), 3.03-2.97 (m, 1H), 2.71 (d, *J* = 5 Hz, 3H), 2.68-2.63 (m, 2H), 2.59-2.50 (m, 1H), 2.14-1.98 (m, 4H), 1.94-1.88 (m, 2H), 1.66-1.51 (m, 4H); ESI-MS (*m/z*): 401 [M + H]⁺; HPLC: method A, 5.97 minutes (97.1%); Anal.

10 Calcd for C₂₃H₂₆F₂N₂O₂·HCl: C, 63.23; H, 6.23; N, 6.41. Found: C, 62.94; H, 6.56; N, 6.32.

EXAMPLE 41

- (a) 6-(*trans*-4-[3-(2,4-Dimethylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one
- 15 (b) 6-(*trans*-{4-[Methyl(2,4-dimethylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one



Step 1: Coupling of 5 and 3-(2,4-dimethylphenyl)-1-propylamine, using the method given in Example 1, gave 6-(*trans*-[3-(2,4-dimethylphenyl)-propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (684 mg, 41%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.12 (d, *J* = 1 Hz, 1H), 7.01-6.88 (m, 5H), 3.50-3.20 (br

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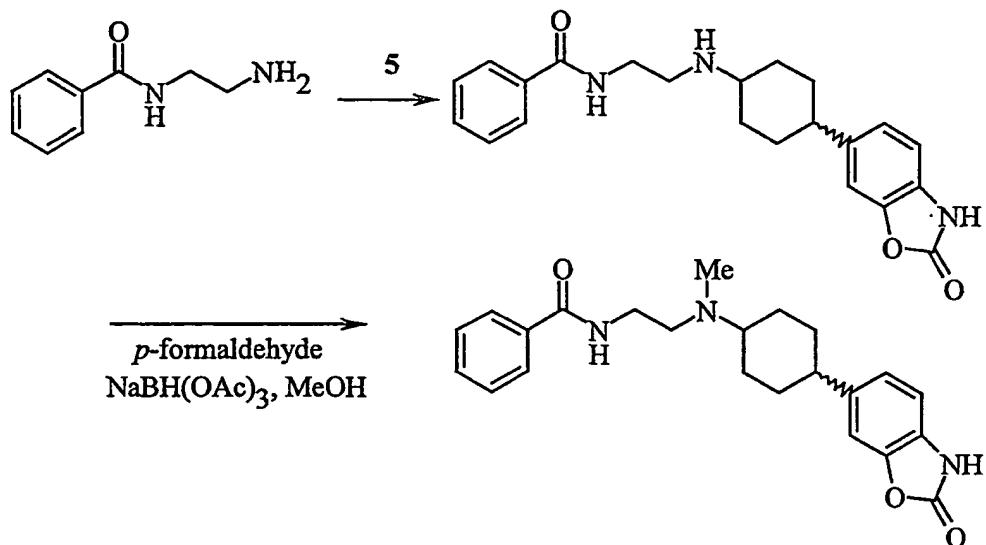
s, 2H), 2.59 (dd, $J = 7, 7$ Hz, 2H), 2.55 (dd, $J = 7, 7$ Hz, 2H), 2.49-2.39 (m, 2H), 2.22 (s, 3H), 2.21 (s, 3H), 1.98-1.92 (m, 2H), 1.81-1.75 (m, 2H), 1.65-1.59 (m, 2H), 1.44 (dddd, $J = 10, 10, 10, 3$ Hz, 2H), 1.13 (dddd, $J = 10, 10, 10, 3$ Hz, 2H).

Step 2: 6-(*trans*-4-[3-(2,4-Dimethylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (400 mg, 1.0 mmol) was coupled with *p*-formaldehyde (740 mg, 24.7 mmol) following the procedure described in Example 17, except CH₂Cl₂ (15 mL) was also added. Formation of the HCl salt gave 6-(*trans*-{4-[methyl(2,4-dimethylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one (247 mg, 51%), as a white solid: mp 219-223°C; IR (KBr): 2944, 1770 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.51 (s, 1H), 10.14 (s, 1H), 7.17 (s, 1H), 7.06 (d, $J = 8$ Hz, 1H), 7.00 (s, 2H), 6.98 (s, 1H), 6.94 (d, $J = 8$ Hz, 1H), 3.35-3.30 (m, 1H), 3.22-3.15 (m, 1H), 3.09-3.01 (m, 1H), 2.70 (d, $J = 5$ Hz, 3H), 2.61-2.52 (m, 3H), 2.25 (s, 3H), 2.23 (s, 3H), 2.16-2.07 (m, 2H), 1.98-1.87 (m, 4H), 1.68-1.51 (m, 4H); ESI-MS (*m/z*): 393 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₅H₃₂N₂O₂, 393.2542; found, 393.2546; HPLC: method A, 6.40 minutes (99.4%); method B, 12.03 minutes (>99%); Anal. Calcd for C₂₅H₃₂N₂O₂·HCl·0.5H₂O: C, 68.55; H, 7.82; N, 6.40. Found: C, 68.32; H, 8.03; N, 6.74.

EXAMPLE 42

- (a) *N*-(2-{Methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-ethyl)benzamide
(b) *N*-{2-[4-(2-Oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexylamino]ethyl}-benzamide

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Step 1: Coupling of ketone 5 and *N*-(2-aminoethyl)benzamide, using the method given in Example 1, followed by conversion to the HCl salt gave *N*-(2-{methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}ethyl)-

5 benzamide (1.58 g, 58%) as a white solid (a mixture of *cis/trans* isomers): ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.84 (br s, 0.6H), 8.77 (br s, 1.4H), 7.92 (d, *J*= 7 Hz, 2H), 7.56-7.48 (m, 3H), 7.34 (br s, 0.3H), 7.18 (s, 0.7H), 7.10 (d, *J*= 8 Hz, 0.3H), 7.02-6.98 (m, 2.7H), 3.63-3.58 (m, 2H), 3.13-3.11 (m, 3H), 2.16 (m, 2H), 1.98-1.87 (m, 2H), 1.75-1.72 (m, 0.6H), 1.62-1.60 (m, 0.6H), 1.55-10 1.46 (m, 4.8H); ESI-MS (*m/z*): 380 [M + H]⁺.

Step 2: Coupling of *N*-(2-{methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}ethyl)benzamide (755 mg, 1.81 mmol) and *p*-formaldehyde (0.50 mL of a 37 wt% aqueous solution, 6.1 mmol), following the procedure described in Example 17 except NaOH (1.8 mL of a 1.0N aqueous solution, 15 1.8 mmol) and CH₂Cl₂ (5 mL) were added, gave *N*-(2-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexylamino]ethyl)benzamide (528 mg, 66%), as a white solid (a mixture of *cis/trans* isomers): mp 167-175°C; IR (KBr): 2940, 1770, 1647 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.51 (s, 1H), 10.41 (br s, 0.7H), 10.03 (br s, 0.3H) 8.96-8.94 (m, 1H), 8.00-7.92 (m, 2H), 7.60-7.40 (m, 3H), 7.15 (s, 1H), 7.00 (s, 1H), 3.79-3.65 (m, 2H), 3.45-3.19 (m, 2H), 2.82-2.79 (m, 4H), 2.58-2.50 (m, 1H), 2.20-2.10 (m, 2H), 1.92-1.81 (m, 3H), 1.70-1.60 (m, 2H).

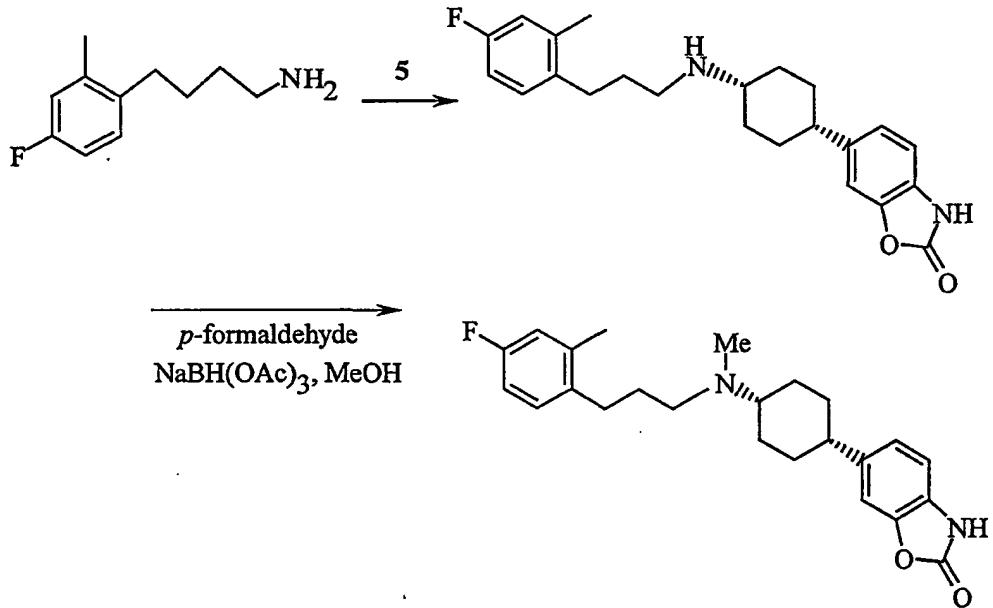
-79-

1.51 (m, 4H); ESI-MS (*m/z*): 394 [M + H]⁺; HPLC: method A, 4.89 minutes (95.0%); method B, 10.0 minutes (>99%); Anal. Calcd for C₂₃H₂₇FN₃O₃·HCl·0.75H₂O: C, 62.30; H, 6.71; N, 9.48. Found: C, 62.43; H, 6.68; N, 9.62.

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EXAMPLE 43

- (a) 6-(*trans*-4-[3-(4-Fluoro-2-methylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one; and
 (b) 6-(*trans*-{4-[Methyl(4-fluoro-2-methylphenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one



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Step 1: Coupling of ketone 5 and 3-(4-fluoro-2-methylphenyl)-1-propylamine, using the method given in Example 1, gave 6-(*trans*-4-[3-(4-fluoro-2-methylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one (630 mg, 56%) as the HCl salt: ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 8.88 (s, 2H), 7.22-7.13 (m, 2H), 7.05-6.91 (m, 4H), 3.09-2.87 (m, 3H), 2.67-2.62 (m, 3H), 2.30 (s, 3H), 2.17-2.13 (m, 2H), 1.92-1.79 (m, 4H), 1.58-1.41 (m, 4H).

Step 2: 6-(*trans*-4-[3-(4-Fluoro-2-methylphenyl)propylamino]-cyclohexyl)-3*H*-benzoxazol-2-one (600 mg, 1.4 mmol) was coupled with *p*-formaldehyde (1.1 g, 37 mmol), following the procedure described in Example 17, gave 6-(*trans*-{4-[methyl(4-fluoro-2-methylphenylpropyl)amino]-

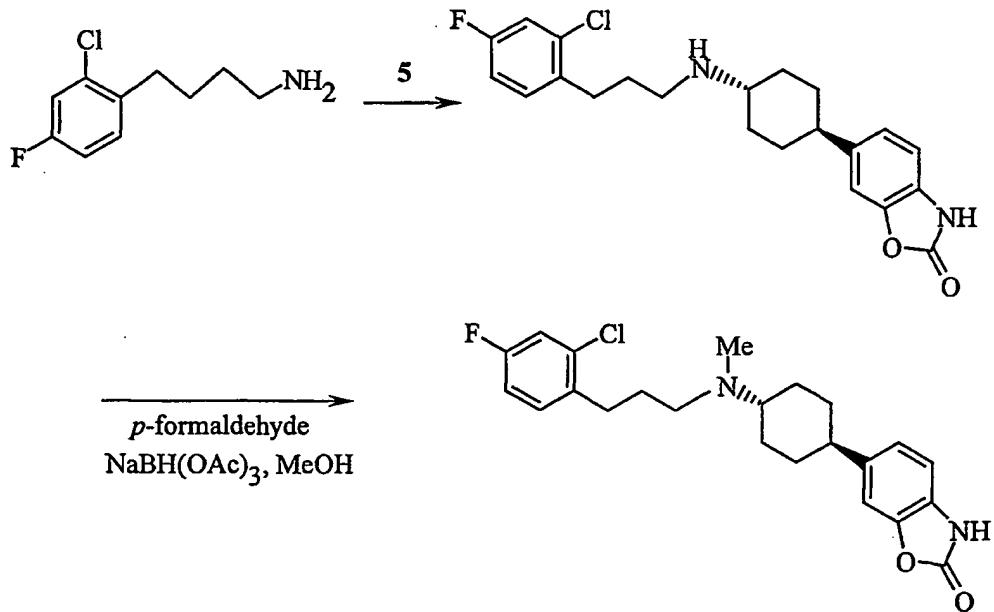
-80-

cyclohexyl})-3*H*-benzoxazol-2-one (226 mg, 52%), as the HCl salt: mp 266-279°C; IR (KBr): 2950, 1768 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 10.20 (s, 1H), 7.24-7.20 (m, 1H), 7.17 (s, 1H), 7.04-6.94 (m, 4H), 3.32-3.30 (m, 1H), 3.21-3.02 (m, 2H), 3.15-3.02 (m, 1H), 2.70 (br s, 3H), 2.63-2.52 (m, 2H), 2.30 (s, 3H), 2.18-2.07 (m, 2H), 1.99-1.88 (m, 4H), 1.69-1.51 (m, 4H); ESI-MS (*m/z*): 397 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₄H₂₉FN₂O₂, 397.2291; found, 397.2296; HPLC: method A, 5.99 minutes (99.0%); method B, 11.81 minutes (>99%); Anal. Calcd for C₂₄H₂₉FN₂O₂·HCl·0.25H₂O: C, 65.89; H, 7.03; N, 6.40. Found: C, 65.93; H, 7.10; N, 6.37.

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EXAMPLE 44

- (a) 6-{*trans*-4-[3-(2-Chloro-4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one; and
 (b) 6-{*trans*-4-{[3-(2-Chloro-4-fluorophenyl)propyl]methylamino}cyclohexyl}-3*H*-benzoxazol-2-one



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Step 1: Condensation of 3-(2-chloro-4-fluorophenyl)-1-propylamine (1.5 g, 6.5 mmol) and ketone 5 (1.5 g, 6.5 mmol), following the procedure described in Example 1, gave 6-{*trans*-4-[3-(2-chloro-4-fluorophenyl)-propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (535 mg, 21%), as a white solid:

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¹H NMR (500 MHz, DMSO-d₆): δ 7.41-7.35 (m, 2H), 7.17-7.13 (m, 2H), 6.99-6.94 (m, 2H), 3.60-2.90 (br s, 2H), 2.72 (t, J = 8 Hz, 2H), 2.59 (t, J = 8 Hz, 2H), 2.49-2.40 (m, 2H), 1.95 (br d, J = 12 Hz, 2H), 1.77 (br d, J = 12 Hz, 2H), 1.69-1.66 (m, 2H), 1.44 (dddd, J = 13, 13, 13, 3 Hz, 2H), 1.13 (dddd, J = 13, 13, 13, 3 Hz, 2H).

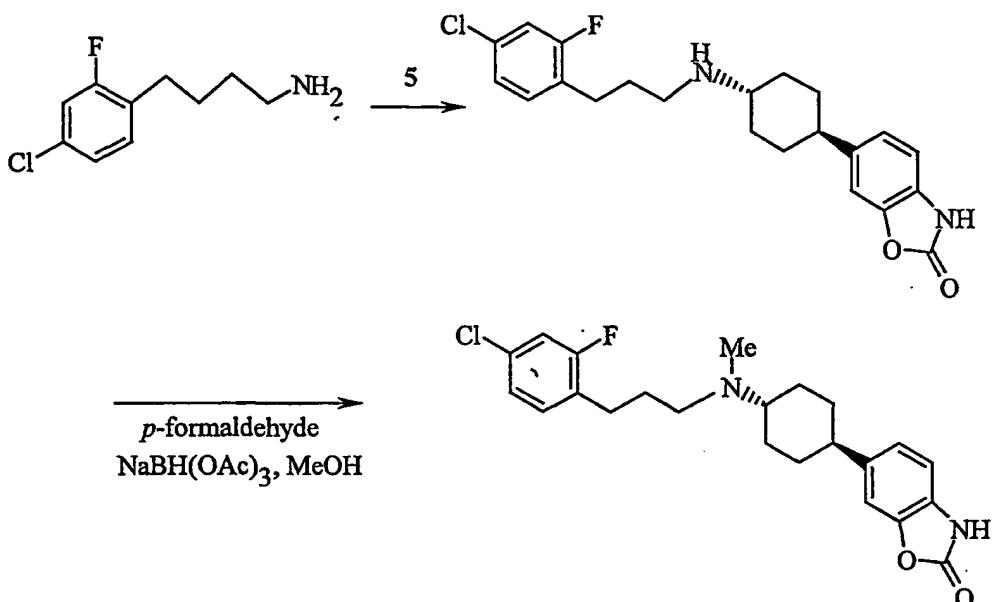
Step 2: Condensation of 6-{*trans*-4-[3-(2-chloro-4-fluorophenyl)-propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (530 mg, 1.3 mmol) and *p*-formaldehyde (0.43 mL of a 37 wt% solution in H₂O, 5.3 mmol), following the procedure described Example 17, followed by conversion to the HCl salt, gave 6-(*trans*-4-{[3-(2-chloro-4-fluorophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one (226 mg, 38%), as a white solid: mp 256-262°C; IR (KBr): 2948, 1770, 1492, 1451 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆): δ 11.49 (s, 1H), 10.05 (s, 1H), 7.49-7.42 (m, 2H), 7.24-7.19 (m, 1H), 7.17 (br s, 1H), 7.00 (d, J = 1 Hz, 2H), 3.35-3.29 (m, 1H), 3.24-3.18 (m, 1H), 3.11-3.03 (m, 1H), 2.84-2.70 (m, 5H), 2.59-2.51 (m, 1H), 2.18-1.88 (m, 6H), 1.69-1.51 (m, 4H); ESI (*m/z*): 417 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₃H₂₆ClFN₂O₂, 417.1745; found, 417.1748; HPLC: method A, 5.88 minutes (>99%); method B, 12.00 minutes (>99%); Anal. Calcd for C₂₃H₂₆ClFN₂O₂·HCl·0.25H₂O: C, 60.33; H, 6.05; N, 6.12. Found: C, 60.35; H, 6.08; N, 5.93.

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EXAMPLE 45

- (a) 6-{*trans*-4-[3-(4-Chloro-2-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one
- (b) 6-(*trans*-4-{[3-(4-Chloro-2-fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one

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**Step 1:** Condensation of 3-(4-chloro-2-fluorophenyl)-1-propylamine

(1.5 g, 6.5 mmol) and ketone 5 (1.5 g, 6.5 mmol), following the procedure described in Example 1, gave 6-{*trans*-4-[3-(4-chloro-2-fluorophenyl)-propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (479 mg, 18%), as a white solid:
¹H NMR (500 MHz, DMSO-*d*₆): δ 7.36-7.32 (m, 2H), 7.22-7.20 (m, 1H), 7.13 (d, J = 1 Hz, 1H), 6.99-6.94 (m, 2H), 3.70-3.00 (br s, 2H), 2.64 (t, J = 8 Hz, 2H), 2.57 (t, J = 8 Hz, 2H), 2.47-2.38 (m, 2H), 1.94 (br d, J = 10 Hz, 2H), 1.77 (br d, J = 10 Hz, 2H), 1.70-1.64 (m, 2H), 1.44 (dd, J = 13, 13, 13, 3 Hz, 2H), 1.13 (dd, J = 13, 13, 13, 3 Hz, 2H).

Step 2: Condensation of 6-{*trans*-4-[3-(4-chloro-2-fluorophenyl)-

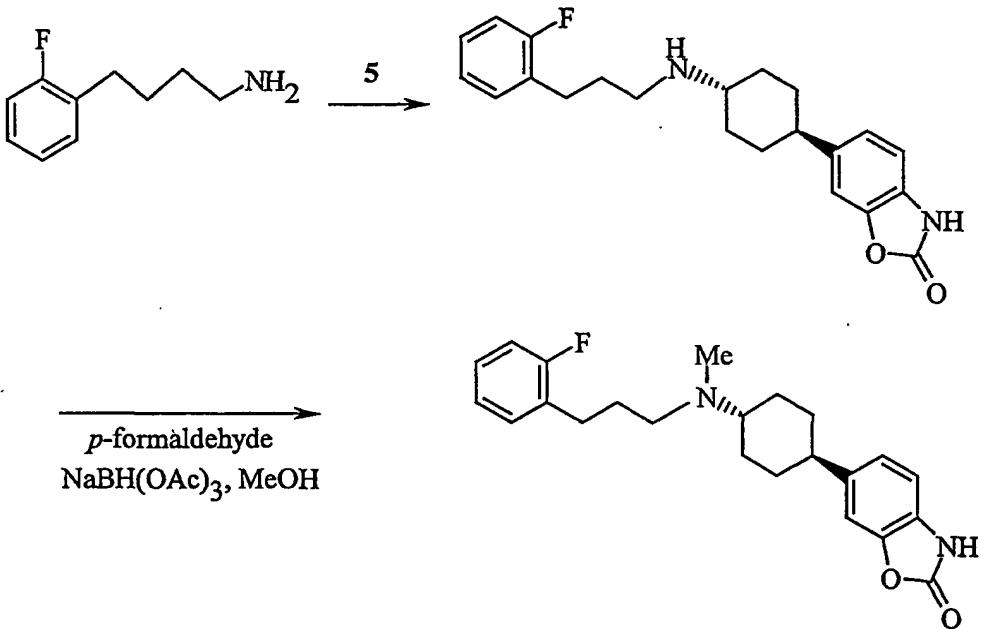
propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (460 mg, 1.1 mmol) and *p*-formaldehyde (0.40 mL of a 37 wt% solution in H₂O, 5.3 mmol), following the procedure described in Example 17 followed by conversion to the HCl salt, gave 6-(*trans*-4-{[3-(4-chloro-2-fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (351 mg, 70%), as a white solid: mp 274-275 °C; IR (KBr): 2950, 1773, 1490, 1452 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 10.32 (s, 1H), 7.43-7.38 (m, 2H), 7.28-7.26 (m, 1H), 7.16 (br s, 1H), 7.00 (d, J = 1 Hz, 2H), 3.33-3.28 (m, 1H), 3.21-3.14 (m, 1H), 3.07-2.99 (m, 1H), 2.74-2.63 (m, 5H), 2.58-2.52 (m, 1H), 2.18-1.96 (m, 4H), 1.93-1.88 (m, 2H), 1.68-

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1.51 (m, 4H); ESI (*m/z*): 417 [M + H]⁺; HPLC: method A, 5.94 minutes (>99%); method B, 12.09 minutes (>99%); Anal. Calcd for C₂₃H₂₆ClFN₂O₂·HCl: C, 60.93; H, 6.00; N, 6.18. Found: C, 60.76; H, 6.09; N, 6.00.

EXAMPLE 46

- 5 (a) 6-{*trans*-4-[3-(2-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one
 (b) 6-(*trans*-4-{[3-(2-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



10 Coupling of ketone 5 and 3-(2-fluorophenyl)-1-propylamine, using the method given in Example 1, gave 6-{*trans*-4-[3-(2-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (1.7 g, 45%) as the HCl salt: ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 8.86 (s, 2H), 7.34 (t, *J* = 8 Hz, 1H), 7.35-7.26 (m, 1H), 7.19-7.15 (m, 3H), 7.02-6.97 (m, 2H), 3.10-3.03 (m, 1H), 2.98-2.92 (m, 2H), 2.72 (dd, *J* = 8, 8 Hz, 2H), 2.57-2.50 (m, 1H), 2.18-2.13 (m, 2H), 1.98-1.92 (m, 2H), 1.89-1.85 (m, 2H), 1.57-1.46 (m, 4H).

15 6-{*trans*-4-[3-(2-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (700 mg, 1.7 mmol) was coupled with *p*-formaldehyde (0.37 g, 12.3 mmol), following the procedure described in Example 17, gave 6-(*trans*-4-{[3-(2-

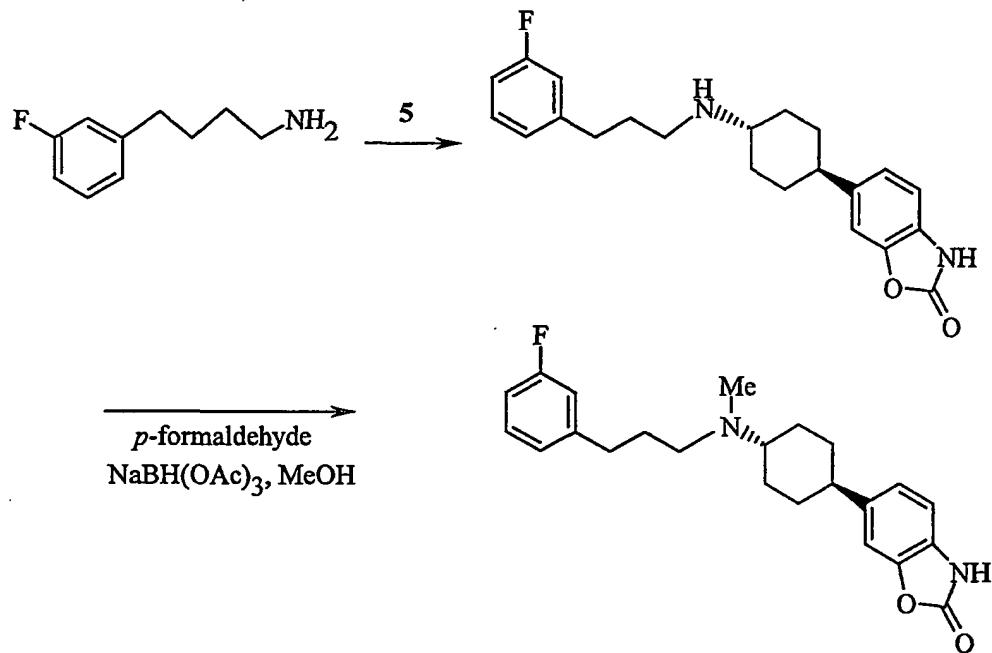
-84-

fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (407 mg, 57%), as the HCl salt: mp 242-246°C; IR (KBr): 2944, 1765 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.52 (s, 1H), 10.42 (s, 1H), 7.39-7.35 (m, 1H), 7.31-7.26 (m, 1H), 7.18-7.15 (m, 3H), 7.00 (s, 2H), 3.34-3.30 (m, 1H), 3.21-3.15 (m, 1H), 3.09-3.01 (m, 1H), 2.69 (d, *J* = 4 Hz, 5H), 2.58-2.51 (m, 1H), 2.18-1.98 (m, 4H), 1.93-1.87 (m, 2H), 1.69-1.51 (m, 4H); ESI-MS (*m/z*): 383 [M + H]⁺; HPLC: method A, 5.66 minutes (99.4%); method B, 11.21 minutes (>99%); Anal. Calcd for C₂₃H₂₇FN₂O₂·HCl·0.25H₂O: C, 65.24; H, 6.78; N, 6.62. Found: C, 65.34; H, 6.65; N, 6.53.

10

EXAMPLE 47

- (a) 6-{*trans*-4-[3-(3-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one
- (b) 6-(*trans*-4-{[3-(3-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



15

Coupling of ketone 5 and 3-(3-fluorophenyl)-1-propylamine, using the method given in Example 1, gave 6-{*trans*-4-[3-(3-fluorophenyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (1.4 g, 37%) as the HCl salt: ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.48 (s, 1H), 8.79 (s, 2H), 7.38-7.33 (m, 1H), 7.17 (s,

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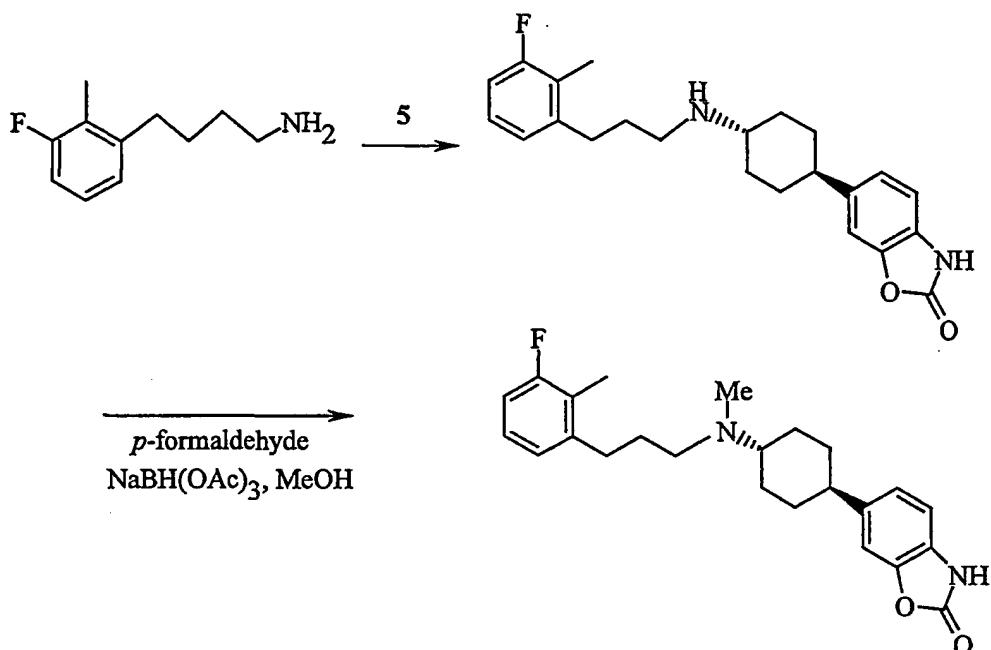
1H), 7.12-7.08 (m, 2H), 7.06-6.97 (m, 3H), 3.10-3.03 (m, 1H), 2.97-2.89 (m, 2H), 2.71 (dd, $J = 8, 8$ Hz, 2H), 2.57-2.50 (m, 1H), 2.18-2.11 (m, 2H), 1.98-1.92 (m, 2H), 1.89-1.85 (m, 2H), 1.57-1.46 (m, 4H).

5 6-<{trans}-4-[3-(3-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (700 mg, 1.7 mmol) was coupled with *p*-formaldehyde (0.37 g, 12.3 mmol), following the procedure described in Example 17, gave 6-(*trans*-4-{[3-(3-fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (381 mg, 54%), as the HCl salt: mp 210-238°C; IR (KBr): 2944, 1763 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.51 (s, 1H), 10.21 (s, 1H), 7.38-7.34 (m, 1H), 7.16 (s, 1H), 7.14-7.09 (m, 2H), 7.04-7.02 (m, 1H), 7.00 (s, 2H), 3.33-3.30 (m, 1H), 3.19-3.11 (m, 1H), 3.05-2.98 (m, 1H), 2.72-2.63 (m, 5H), 2.58-2.51 (m, 1H), 2.18-1.98 (m, 4H), 1.93-1.87 (m, 2H), 1.69-1.51 (m, 4H); ESI-MS (*m/z*): 383 [M + H]⁺; HPLC: method A, 5.75 minutes (99.0%); Anal. Calcd for C₂₃H₂₇FN₂O₂·HCl: C, 65.94; H, 6.74; N, 6.69. Found: C, 65.72; H, 6.77; N, 6.68.

EXAMPLE 48

- (a) 6-{*trans*-4-[3-(3-Fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one
 (b) 6-({*trans*-4-[[3-(3-Fluoro-2-methylphenyl)propyl]methylamino]cyclohexyl}-3*H*-benzoxazol-2-one

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Coupling of ketone 5 and 3-(2-methyl-3-fluorophenyl)-1-propylamine, using the method given in Example 1, gave 6-{*trans*-4-[3-(3-fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (1.4 g, 56%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.16-7.10 (m, 2H), 7.01-6.93 (m, 4H), 2.65 (dd, *J* = 8, 8 Hz, 2H), 2.60 (dd, *J* = 7, 7 Hz, 2H), 2.49-2.39 (m, 2H), 2.18 (d, *J* = 2 Hz, 3H), 1.98-1.93 (m, 2H), 1.81-1.75 (m, 2H), 1.68-1.61 (m, 2H), 1.45 (dd, *J* = 13, 13, 13, 3 Hz, 2H), 1.13 (dd, *J* = 13, 13, 13, 3 Hz, 2H).

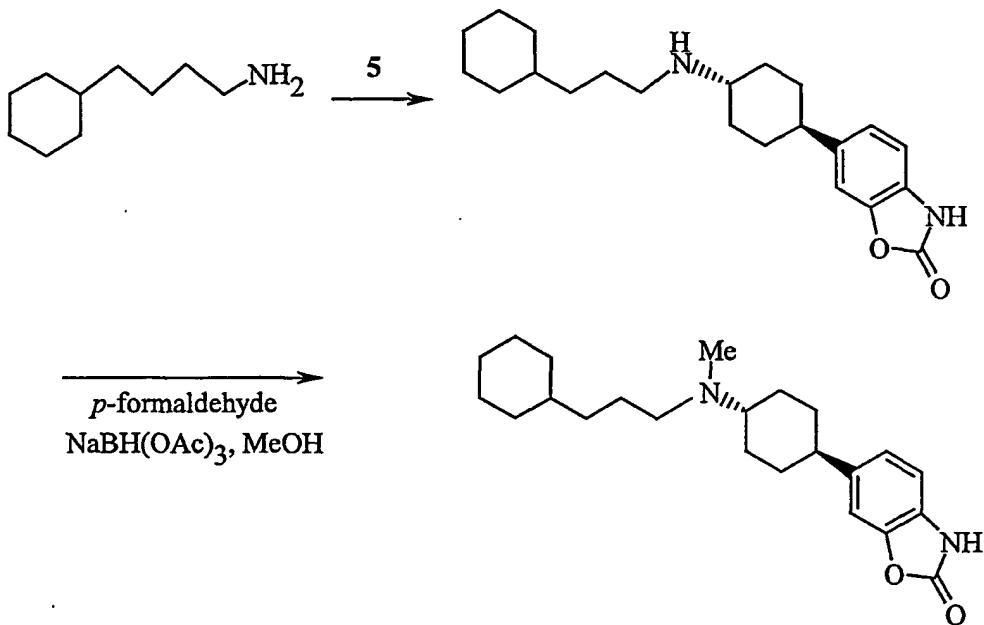
6-{*trans*-4-[3-(3-Fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (700 mg, 1.7 mmol) was coupled with *p*-formaldehyde (1.48 g, 49.3 mmol), following the procedure described in Example 17, gave 6-(*trans*-4-{[3-(3-fluoro-2-methylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (432mg, 55%), as the HCl salt: mp 264-269°C; IR (KBr): 2947, 1769 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 10.02 (s, 1H), 7.21-7.15 (m, 2H), 7.07-6.99 (m, 4H), 3.35-3.30 (m, 1H), 3.25-3.18 (m, 1H), 3.11-3.05 (m, 1H), 2.71 (d, *J* = 5 Hz, 3H), 2.70-2.62 (m, 2H), 2.58-2.51 (m, 1H), 2.20 (d, *J* = 2 Hz, 3H), 2.17-2.07 (m, 2H), 2.00-1.88 (m, 4H), 1.69-1.51 (m, 4H); ESI-MS (*m/z*): 397 [M + H]⁺; HPLC: method A, 6.09 minutes (98.3%); method B, 11.66 minutes

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(>99%); Anal. Calcd for $C_{24}H_{29}FN_2O_2 \cdot HCl \cdot 0.25H_2O$: C, 65.89; H, 7.03; N, 6.40. Found: C, 66.01; H, 6.85; N, 6.35.

EXAMPLE 49

- 5
- (a) 6-{*trans*-4-[*(3-Cyclohexylpropyl)amino*]cyclohexyl}-3*H*-benzoxazol-2-one
 - (b) 6-{*trans*-4-[*(3-Cyclohexylpropyl)methylamino*]cyclohexyl}-3*H*-benzoxazol-2-one



10

Step 1: Condensation of cyclohexyl-1-propylamine (0.9 g, 6.4 mmol) and ketone 5 (1.5 g, 6.4 mmol), following the procedure described in Example 1, gave 6-{*trans*-4-[*(3-cyclohexylpropyl)amino*]cyclohexyl}-3*H*-benzoxazol-2-one (352 mg, 15%), as a white solid: 1H NMR (500 MHz, DMSO-*d*₆): δ 7.12 (br s, 1H), 6.97-6.93 (m, 2H), 3.70-3.10 (br s, 2H), 2.53 (t, *J* = 7 Hz, 2H), 2.48-2.39 (m, 2H), 1.95 (br d, *J* = 12 Hz, 2H), 1.77 (br d, *J* = 12 Hz, 2H), 1.70-1.59 (m, 5H), 1.50-1.38 (m, 4H), 1.23-1.08 (m, 8H), 0.90-0.81 (m, 2H).

15

Step 2: Condensation of 6-{*trans*-4-[*(3-cyclohexylpropyl)amino*]-cyclohexyl}-3*H*-benzoxazol-2-one (350 mg, 0.98 mmol) and *p*-formaldehyde (0.40 mL of a 37 wt% solution in H₂O, 4.9 mmol), following the procedure described in Example 17 followed by conversion to the HCl salt, gave 6-{*trans*-4-[*(3-cyclohexylpropyl)methylamino*]cyclohexyl}-3*H*-benzoxazol-2-one (235 mg,

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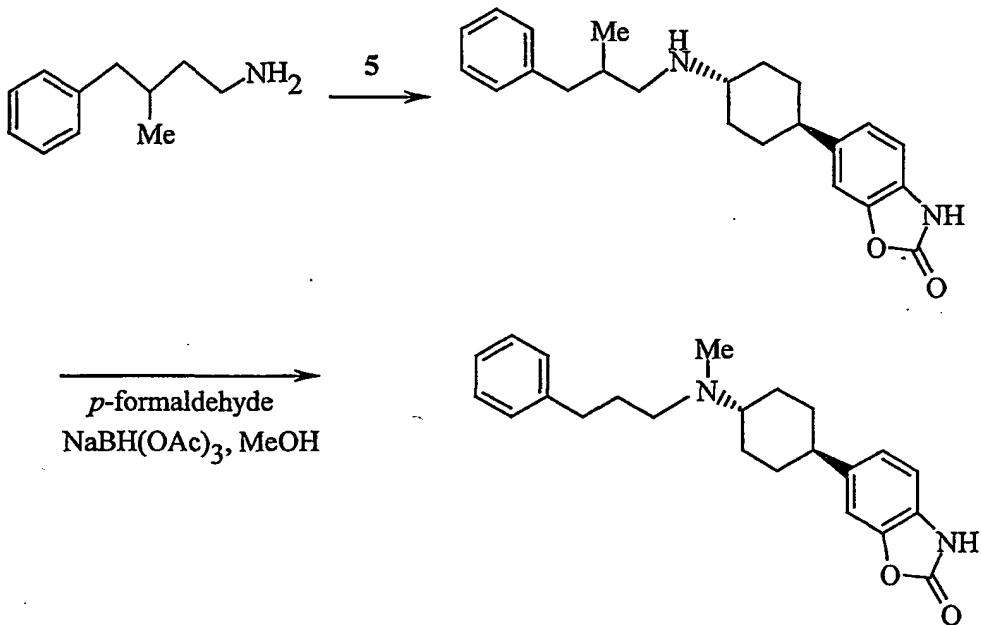
58%), as a white solid: mp 247-251°C; IR (KBr): 2931, 1771, 1502, 1451 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 10.12 (s, 1H), 7.16 (s, 1H), 7.00 (s, 2H), 3.32-3.25 (m, 1H), 3.11-3.04 (m, 1H), 2.99-2.91 (m, 1H), 2.67 (d, J = 5 Hz, 3H), 2.59-2.52 (m, 1H), 2.18-2.08 (m, 2H), 1.94-1.88 (m, 2H), 1.76-1.51 (m, 11 H), 1.29-1.09 (m, 6H), 0.93-0.85 (m, 2H); ESI (*m/z*): 371 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₃H₃₄N₂O₂, 371.2698; found, 371.2708; HPLC: method A, 6.32 minutes (99.0%); method B, 12.58 minutes (>99%); Anal. Calcd for C₂₃H₃₄N₂O₂·HCl·0.25H₂O: C, 67.13; H, 8.70; N, 6.81. Found: C, 67.24; H, 8.65; N, 6.73.

10

EXAMPLE 50

(a) 6-{*trans*-[4-(2-Methyl-3-phenylpropylamino)cyclohexyl]}-3*H*-benzoxazol-2-one

(b) 6-{*trans*-{4-[Methyl(2-methyl-3-phenylpropyl)amino]cyclohexyl}}-3*H*-benzoxazol-2-one



15

Step 1: Condensation of 2-methyl-3-phenylpropylamine (830 mg, 3.97 mmol) and ketone 5 (918 mg, 3.97 mmol), following the procedure described in Example 1, gave compound 6-{*trans*-[4-(2-methyl-3-phenylpropylamino)cyclohexyl]}-3*H*-benzoxazol-2-one (400 mg, 48%): ¹H NMR (500 MHz, DMSO-

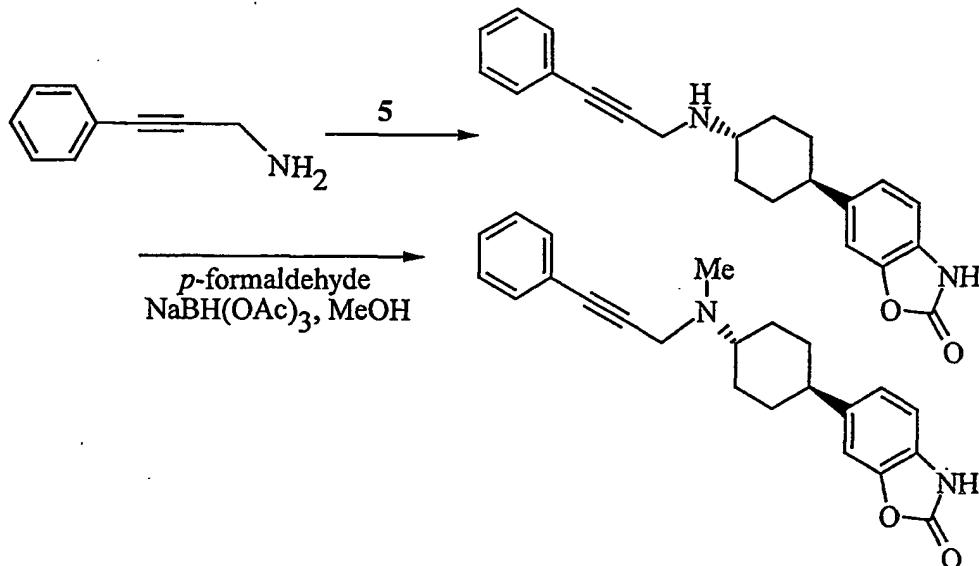
-89-

d₆): δ 7.32-7.21 (m, 2H), 7.19-7.17 (m, 4H), 7.03-6.98 (m, 2H), 2.77 (dd, *J* = 13, 6 Hz, 1H), 2.55-2.34 (m, 7H), 1.99-1.97 (m, 2H), 1.84-1.80 (m, 2H), 1.50-1.47 (m, 2H), 1.18-1.05 (m, 2H), 0.88 (d, *J* = 6 Hz, 3H).

Step 2: Condensation of 6-{*trans*-[4-(2-methyl-3-phenylpropylamino)-cyclohexyl]}-3*H*-benzoxazol-2-one (400 mg, 1.10 mmol) and *p*-formaldehyde (0.50 mL of a 37 wt% solution in H₂O, 2.4 mmol), following the procedure described in Example 17, gave 6-(*trans*-{4-[methyl(2-methyl-3-phenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one (200 mg, 52%), as a white foam:
 mp 43-48°C; IR (film): 2927, 1776, 1495, 1450 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.28-7.25 (m, 2H), 7.17-7.15 (m, 4H), 7.00-6.95 (m, 2H), 2.78 (dd, *J* = 13, 5 Hz, 1H), 2.46-2.41 (m, 1H), 2.29-2.14 (m, 6H), 1.83-1.78 (m, 6H), 1.49-1.34 (m, 4H), 0.76 (d, *J* = 6 Hz, 3H); ESI (*m/z*): 379 [M + H]⁺; HPLC: method A, 5.96 minutes (>99%); method B, 10.99 minutes (97.1%); Anal. Calcd for C₂₄H₃₀N₂O₂·0.125H₂O: C, 75.51; H, 8.25; N, 7.34. Found: C, 75.26; H, 7.88; N, 7.20.

EXAMPLE 51

- (a) 6-{*trans*-[4-(3-Phenyl-prop-2-ynylamino)cyclohexyl]}-3*H*-benzoxazol-2-one
- (b) 6-(*trans*-{4-[Methyl(3-phenyl-prop-2-ynyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one



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Step 1: Condensation of 3-phenyl-prop-2-ynylamine (1.0 g, 7.6 mmol) and ketone **5** (1.7 g, 7.6 mmol), following the procedure described in Example 1, except THF was used as solvent gave compound 6-{*trans*-[4-(3-phenyl-prop-2-ynylamino)cyclohexyl]}-3*H*-benzoxazol-2-one (400 mg, 58%) as a white solid:

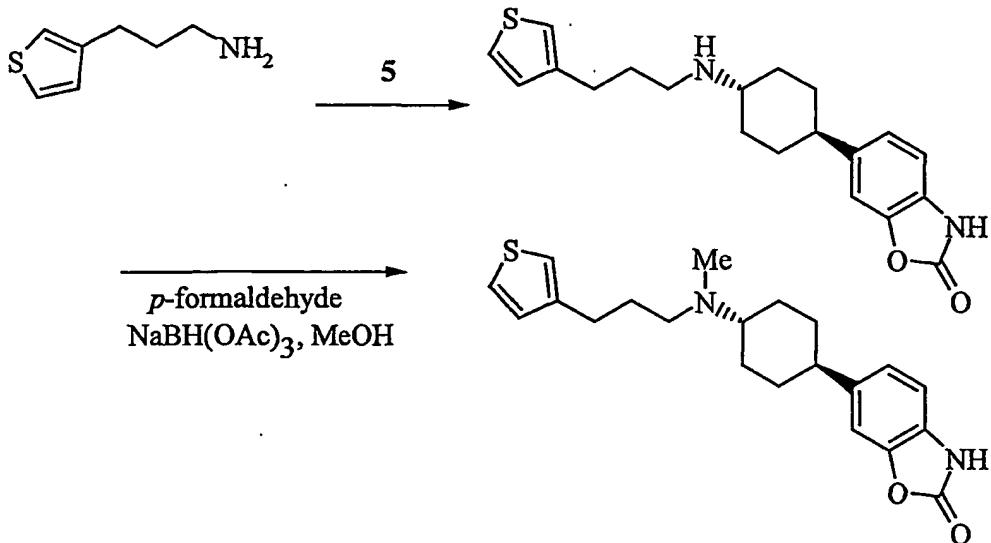
5 ^1H NMR (500 MHz, DMSO-*d*₆): δ 7.45-7.35 (m, 5H), 7.19 (s, 1H), 7.50-6.94 (m, 2H), 3.59 (s, 2H), 3.30 (m, 2H), 2.75-2.61 (m, 1H), 2.06-2.00 (m, 2H), 1.85-1.80 (m, 2H), 1.58-1.41 (m, 2H), 1.25-1.10 (m, 2H).

10 **Step 2:** Condensation of 6-{*trans*-[4-(3-phenyl-prop-2-ynylamino)-cyclohexyl]}-3*H*-benzoxazol-2-one (400 mg, 1.20 mmol) and *p*-formaldehyde (180 mg of a 37 wt% solution in H₂O, 6.0 mmol), following the procedure described in Example 17, gave 6-(*trans*-{4-[methyl(3-phenyl-prop-2-ynyl)-amino]cyclohexyl})-3*H*-benzoxazol-2-one (100 mg, 65%), as a white solid: mp 249-252°C; IR (KBr): 2938, 2627, 1770 cm⁻¹; ^1H NMR (500 MHz, DMSO-*d*₆): δ 7.55 (d, *J* = 6 Hz, 2H), 7.47-7.43 (m, 2H), 7.20 (s, 1H), 7.03-6.98 (m, 2H), 4.38 (s, 2H), 3.42-3.33 (m, 3H), 2.86 (s, 3H), 2.56-2.50 (m, 1H), 2.22 (m, 2H), 1.94 (brd, *J* = 11 Hz, 2H), 1.71-1.67 (m, 2H), 1.57-1.55 (m, 2H); HRMS-APCI (m/z): [M + H]⁺ calcd for C₂₃H₂₅N₂O₂, 361.1916; found, 361.1914; HPLC: method A, 5.74 minutes (>99%); method B, 11.03 minutes (>99%); Anal. Calcd for C₂₃H₂₄N₂O₂·HCl·0.5H₂O: C, 68.06; H, 6.46; N, 6.90. Found: C, 67.81; H, 6.65; N, 6.74.

EXAMPLE 52

- (a) 6-{*trans*-4-[4-(3-Thiophen-3-yl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one
25 (b) 6-[*trans*-4-{[3-(3-Thiophen-3-yl)propyl]methylamino}cyclohexyl]-3*H*-benzoxazol-2-one

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Step 1: Condensation of (3-thienyl)-1-propylamine (2.8 g, 20.0 mmol) and ketone 5 (4.6 g, 20.0 mmol), following the procedure described in Example 1, gave compound 6-{*trans*-4-[4-(3-thienyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one (410 mg, 5%), as a white solid: ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.43-7.41 (m, 1H), 7.14-7.12 (m, 2H), 7.00-6.93 (m, 3H), 3.60-3.10 (br s, 2H), 2.63 (t, *J*= 7 Hz, 2H), 2.58 (t, *J*= 7 Hz, 2H), 2.49-2.39 (m, 2H), 1.95 (br d, *J*= 11 Hz, 2H), 1.78 (br d, *J*= 11 Hz, 2H), 1.73-1.68 (m, 2H), 1.45 (dd, *J*= 13, 13, 13, 3 Hz, 2H), 1.13 (dd, *J*= 13, 13, 13, 3 Hz, 2H).

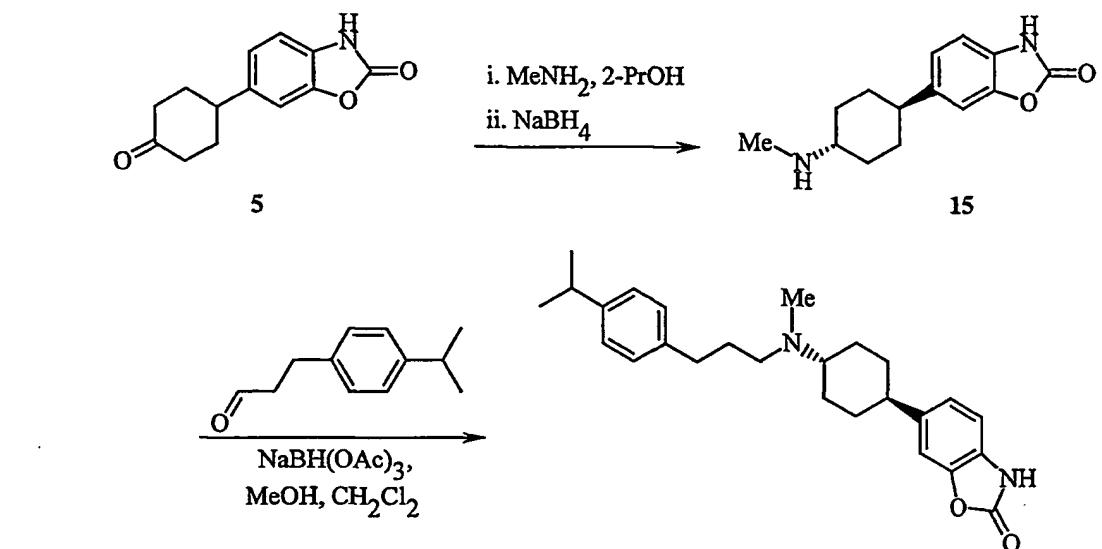
Step 2: Condensation of 6-{*trans*-4-[4-(3-thienyl)propylamino]-cyclohexyl}-3*H*-benzoxazol-2-one (400 mg, 1.0 mmol) and *p*-formaldehyde (0.17 mL of a 37 wt% solution in H₂O, 2.0 mmol), following the procedure described in Example 17, followed by conversion to the HCl salt, gave 6-[*trans*-4-{[3-(3-thienyl)propyl]methylamino}cyclohexyl]-3*H*-benzoxazol-2-one (301 mg, 74%), as a white solid: mp 246-248°C; IR (KBr): 2950, 1759, 1496, 1451 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.47 (s, 1H), 10.09 (s, 1H), 7.50-7.48 (m, 1H), 7.25-7.24 (m, 1H), 7.16 (s, 1H), 7.05-7.04 (m, 1H), 7.00 (s, 2H), 3.34-3.28 (m, 1H), 3.19-3.10 (m, 1H), 3.05-2.98 (m, 1H), 2.71 (d, *J*= 5 Hz, 3H), 2.69-2.65 (m, 2H), 2.58-2.51 (m, 1H), 2.15-2.00 (m, 4H), 1.94-1.88 (m, 2H), 1.68-1.51 (m, 4H); ESI (*m/z*): 371 [M + H]⁺; HPLC: method B, 10.79 minutes (>99%).

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Anal. Calcd for C₂₁H₂₆N₂O₂S·HCl: C, 61.98; H, 6.69; N, 6.88. Found: C, 61.64; H, 6.79; N, 6.70.

EXAMPLE 53

6-(*trans*-4-{[3-(4-Isopropylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



Step 1: To a suspension of ketone **5** (10.4 g, 0.045 mol) in 2-PrOH (520 mL) was added methylamine (33.7 mL of a 2.0 M solution in THF, 0.067 mol). A clear, amber solution formed after ca 15 minutes, and a precipitate gradually formed a few minutes later. After 1.5 hours, the reaction mixture was cooled in an ice/water bath, NaBH₄ (2.6 g, 0.067 mol) was added, and stirring was continued at 0°C for 35 minutes. The reaction mixture was stirred at room temperature for 15 hours. MeOH (ca 2 mL) was added to quench any excess NaBH₄ (no gas evolution was observed), and the solvents were removed under reduced pressure. The residue was partitioned between 1N HCl (500 mL) and EtOAc (250 mL). The aqueous layer was separated, adjusted to pH 7-8 with solid NaHCO₃, and washed with EtOAc (200 mL). A precipitate formed during the wash, which was collected by vacuum filtration and dried to give 6-[*trans*-4-(methylamino)cyclohexyl]-3*H*-benzoxazol-2-one **15** (5.0 g, 46%). The organic layer was separated, and TLC analysis (89:10:1 CH₂Cl₂:MeOH:NH₄OH) showed it contained compound **15**. Compound **15** was also shown by TLC analysis to be

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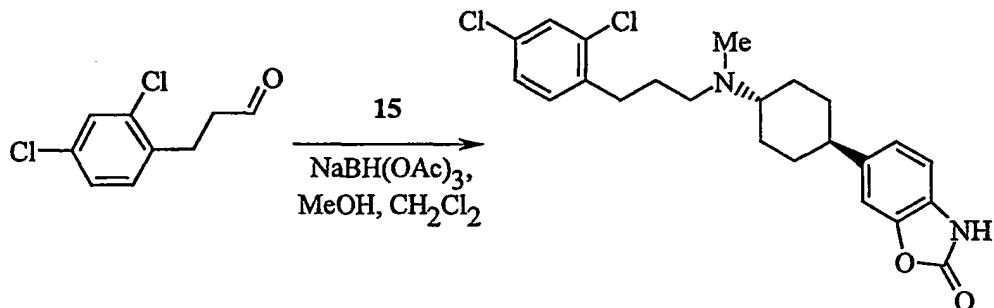
present in the initial EtOAc extraction. The organic extracts were combined, concentrated under reduced pressure, dissolved in a minimal amount of MeOH, and a solid was precipitated out with diethyl ether. The solid was collected by vacuum filtration and dried to give 15 (1.6 g, 13%) as the HCl salt. To the aqueous layer (ca 1L), which also showed the presence of additional 15 by TLC, was added solid NaCl (ca 80 g), and the solution was concentrated under reduced pressure to approximately half its original volume. A solid formed and was collected by vacuum filtration and dried to give 15 (1.3 g, 12%). The solids were combined to give 6-[*trans*-4-(methylamino)cyclohexyl]-3*H*-benzoxazol-2-one 15 (7.9 g, 73%): ^1H NMR (500 MHz, CD₃OD): δ 7.10 (d, J = 1.5 Hz, 1H), 7.03 (dd, J = 8, 1.5 Hz, 1H), 6.98 (d, J = 8 Hz, 1H), 2.67-2.52 (m, 2H), 2.49 (s, 3H), 2.15-2.12 (m, 2H), 1.97-1.94 (m, 2H), 1.61-1.52 (m, 2H), 1.38-1.30 (m, 2H).

Step 2: To a solution of amine 15 (670 mg, 2.40 mmol) in 1:1 CH₂Cl₂:MeOH (30 mL) was added solid NaHCO₃ (200 mg, 2.40 mmol) and, after 10 minutes, 3-(4-isopropylphenyl)propionaldehyde (420 mg, 2.40 mmol). After stirring for 5 minutes, NaBH(OAc)₃ (760 mg, 3.60 mmol) was added, and the mixture was stirred at room temperature for 12 hours. The reaction mixture was brought to pH 8 with solid NaOH and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:5 CH₂Cl₂:MeOH followed by 89:10:1 CH₂Cl₂:MeOH:NH₄OH), followed by formation of the HCl salt and recrystallization (MeOH:Et₂O) gave 6-(*trans*-4-{[3-(4-isopropylphenyl)-propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (514 mg, 48%), as a white solid: mp 179-181°C; IR (KBr): 2959, 1771, 1498, 1451 cm⁻¹; ^1H NMR (500 MHz, DMSO-*d*₆): δ 11.48 (s, 1H), 10.10 (s, 1H), 7.17-7.15 (m, 5H), 7.00 (br s, 2H), 3.32-3.29 (m, 1H), 3.19-3.11 (m, 1H), 3.06-2.99 (m, 1H), 2.89-2.83 (m, 1H), 2.70 (d, J = 4 Hz, 3H), 2.63-2.52 (m, 3H), 2.15-1.95 (m, 4H), 1.93-1.87 (m, 2H), 1.66-1.50 (m, 4H), 1.19 (d, J = 7 Hz, 6H); ESI (*m/z*): 407 [M + H]⁺; method B, 12.69 minutes (>99%); Anal. Calcd for C₂₆H₃₄N₂O₂·HCl: C, 70.49; H, 7.96; N, 6.32. Found: C, 70.29; H, 8.05; N, 6.28.

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EXAMPLE 54

*6-(trans-4-{[3-(2,4-Dichlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one*

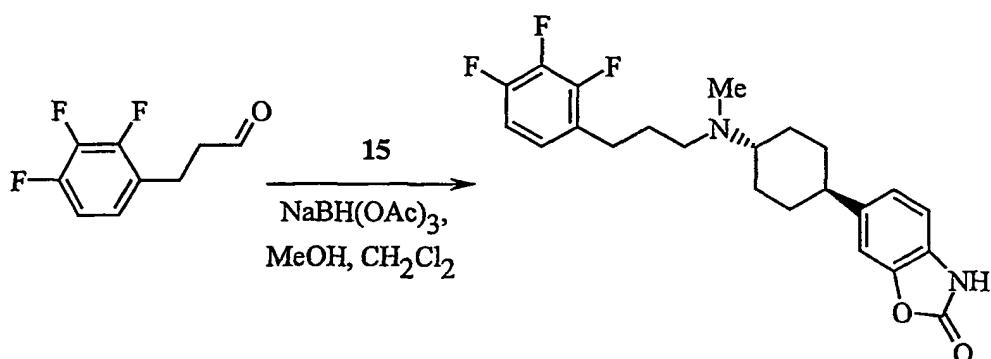


Condensation of 15 (550 mg, 1.9 mmol) and 3-(2,4-dichlorophenyl)-propionaldehyde (390 mg, 1.9 mmol) following the procedure described in Example 45, Step 2, followed by conversion to the HCl salt, gave *6-(trans-4-{[3-(2,4-dichlorophenyl)propyl]methylamino}cyclohexyl)-3H-benzoxazol-2-one* (446 mg, 50%), as an off-white solid: mp 273-279°C; IR (KBr): 2949, 1775, 1500, 1474 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.49 (s, 1H), 10.01 (s, 1H), 7.61 (d, *J* = 2 Hz, 1H), 7.47-7.41 (m, 2H), 7.17 (s, 1H), 7.00 (s, 2H), 3.34-3.29 (m, 1H), 3.22-3.17 (m, 1H), 3.11-3.03 (m, 1H), 2.79-2.73 (m, 2H), 2.71 (d, *J* = 5 Hz, 3H), 2.59-2.48 (m, 1H), 2.14-2.06 (m, 2H), 2.03-1.97 (m, 2H), 1.94-1.88 (m, 2H), 1.69-1.50 (m, 4H); ESI (*m/z*): 433 [M + H]⁺; HPLC: method A, 6.78 minutes (>99%); Anal. Calcd for C₂₃H₂₆Cl₂N₂O₂·HCl: C, 58.80; H, 5.79; N, 5.96. Found: C, 58.62; H, 5.76; N, 5.89.

EXAMPLE 55

*6-(trans-4-{[3-(2,3,4-Trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one*

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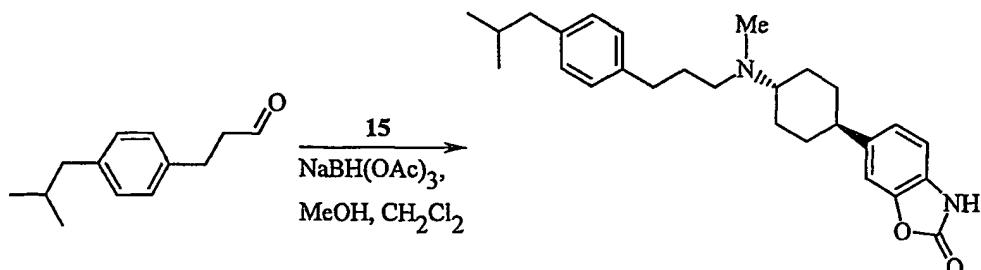


Condensation of 15 (420 mg, 1.5 mmol) and 3-(2,3,4-trifluorophenyl)-propionaldehyde (280 mg, 1.5 mmol), following the procedure described in Example 45, Step 2, followed by conversion to the HCl salt, gave 6-(*trans*-4-{[3-(2,3,4-trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (257 mg, 33%), as an off-white solid: mp 269-274°C; IR (KBr): 2950, 1768, 1513, 1485 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 10.17 (s, 1H), 7.23-7.21 (m, 2H), 7.17 (br s, 1H), 7.00 (d, *J* = 1 Hz, 2H), 3.33-3.26 (m, 1H), 3.21-3.14 (m, 1H), 3.08-3.01 (m, 1H), 2.79-2.71 (m, 2H), 2.69 (d, *J* = 5 Hz, 3H), 2.59-2.50 (m, 1H), 2.16-1.98 (m, 4H), 1.94-1.87 (m, 2H), 1.68-1.50 (m, 4H); HRMS-APCI (*m/z*): [M + H]⁺ calcd for C₂₃H₂₅F₃N₂O₂, 419.1946; found, 419.1948; HPLC: method A, 8.31 minutes (97.7%); method B, 11.85 minutes (97.8%); Anal. Calcd for C₂₃H₂₅F₃N₂O₂·HCl·0.25H₂O: C, 60.13; H, 5.81; N, 6.10. Found: C, 60.14; H, 5.70; N, 6.08.

15

EXAMPLE 56

6-(*trans*-4-{[3-(4-Isobutylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one



Condensation of 15 (1.0 g, 3.6 mmol) and 3-(4-isobutylphenyl)-propionaldehyde (700 mg, 3.6 mmol), following the procedure described in

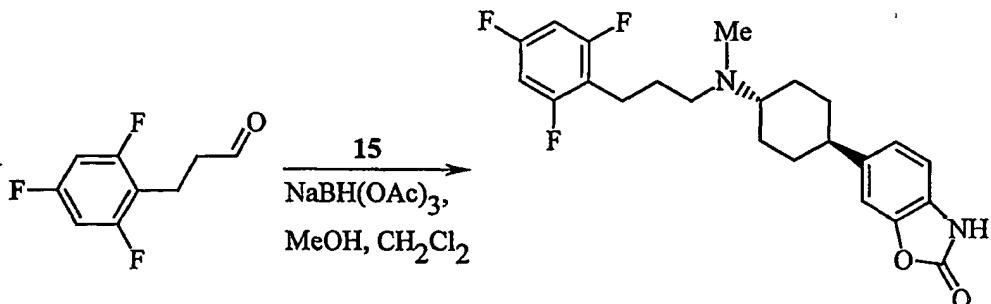
-96-

Example 45, Step 2, followed by conversion to the HCl salt, gave 6-(*trans*-4-{[3-(4-isobutylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (977 mg, 61%), as an off-white solid: mp 162-165°C; IR (KBr): 2953, 1773, 1498, 1451 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.55 (s, 1H), 10.00 (s, 1H), 7.17-5 7.08 (m, 5H), 7.00 (s, 2H), 3.32-3.28 (m, 1H), 3.21-3.08 (m, 1H), 3.08-2.95 (m, 1H), 2.70 (d, *J* = 5 Hz, 3H), 2.65-2.52 (m, 3H), 2.41 (d, *J* = 7 Hz, 2H), 2.14-1.73 (m, 7H), 1.68-1.49 (m, 4H), 0.85 (d, *J* = 7 Hz, 6H); HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₇H₃₆N₂O₂, 421.2855; found, 421.2858; HPLC: method A, 7.49 minutes (>99%); method B, 13.59 minutes (>99%); Anal. Calcd for 10 C₂₇H₃₆N₂O₂·HCl·0.5H₂O: C, 69.58; H, 8.22; N, 6.01. Found: C, 69.23; H, 8.20; N, 5.87.

EXAMPLE 57

6-(*trans*-4-{[3-(2,4,6-Trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one

15



20

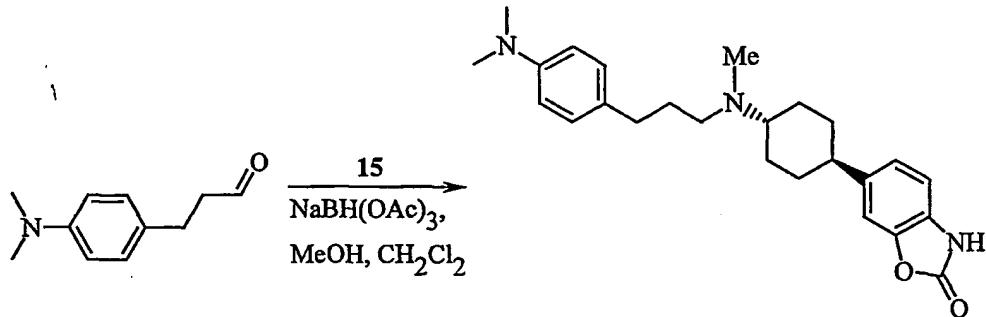
Condensation of 15 (460 mg, 1.9 mmol) and 3-(2,4,6-trifluorophenyl)-propionaldehyde (360 mg, 1.9 mmol), following the procedure described in Example 45, Step 2, followed by conversion to the HCl salt, gave 6-(*trans*-4-{[3-(2,4,6-trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (275 mg, 32%), as a white solid: mp 235-238°C; IR (KBr): 2949, 1772, 1632, 1603 cm⁻¹; ¹H NMR (300 MHz, DMSO-*d*₆): δ 11.54 (s, 1H), 9.78 (s, 1H), 7.26-7.18 (m, 3H), 7.00 (s, 2H), 3.32-3.27 (m, 1H), 3.26-3.04 (m, 2H), 2.71 (d, *J* = 5 Hz, 3H), 2.58-2.54 (m, 1H), 2.66-2.62 (m, 2H), 2.12-1.86 (m, 6H), 1.68-1.48 (m, 4H); ESI (*m/z*): 419 [M + H]⁺; HPLC: method A, 6.30 minutes (98.8%);

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Anal. Calcd for $C_{23}H_{25}F_3N_2O_2 \cdot HCl$: C, 60.73; H, 5.76; N, 6.16. Found: C, 60.43; H, 5.71; N, 5.99.

EXAMPLE 58

5 6-(4-{[3-(*trans*-4-Dimethylaminophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one

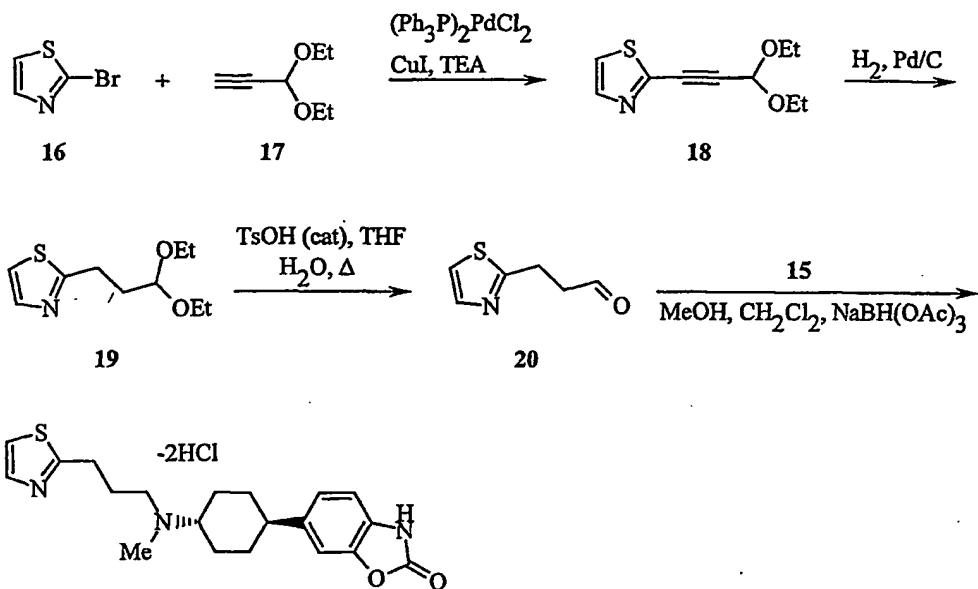


10 Condensation of **15** (2.22 g, 8.41 mmol) and 3-(4-dimethylaminophenyl)-propionaldehyde (910 mg, 5.14 mmol), following the procedure described in Example 45, Step 2, gave 6-(4-{[3-(*trans*-4-dimethylaminophenyl)propyl]-methylamino}cyclohexyl)-3*H*-benzoxazol-2-one (1.63 g, 78%), as an off-white solid: mp 182-184°C; IR (KBr): 2930, 1772, 1491, 1448 cm^{-1} ; ^1H NMR (500 MHz, DMSO-*d*₆): δ 11.4 (br s, 1H), 7.15 (s, 1H), 7.02-6.95 (m, 4H), 6.66 (d, *J* = 9 Hz, 2H), 2.84 (s, 6H), 2.54-2.44 (m, 6H), 2.20 (s, 3H), 1.83-1.81 (m, 4H), 1.68-1.63 (m, 2H), 1.50-1.32 (m, 4H); ESI (*m/z*): 408 [M + H]⁺; HPLC: method A, 4.23 minutes (>99%); method B, 8.36 minutes (>99%); Anal. Calcd for $C_{25}H_{33}N_3O_2 \cdot 0.5H_2O$: C, 72.08; H, 8.23; N, 10.09. Found: C, 72.48; H, 8.09; N, 10.09.

EXAMPLE 59

20 6-{*trans*-4-[Methyl(3-thiazol-2-ylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one

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Step 1: To 2-bromothiazole 16 (5.0 g, 30 mmol) in DMF (40 mL) was added propiolaldehyde diethyl acetal 17 (4.4 g, 34 mmol), CuI (170 mg, 0.90 mmol), and triethylamine (8.4 mL, 60 mmol). The reaction mixture was deoxygenated with argon for 15 minutes, bis(triphenylphosphine)palladium (II) chloride (640 mg, 0.10 mmol) was added, and the mixture was deoxygenated again with argon for 15 minutes. After stirring at ambient temperature for 12 hours and then at 100°C for 2.5 hours, the reaction was cooled to ambient temperature, diluted with EtOAc (500 mL), washed with water (3 × 150 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 75:25 hexanes:EtOAc) gave alkyne 18 (3.4 g, 54%):

10 $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.85 (d, $J = 3$ Hz, 1H), 7.39 (d, $J = 3$ Hz, 1H), 5.52 (s, 1H), 3.88-3.77 (m, 2H), 3.73-3.63 (m, 2H), 1.28 (t, $J = 7$ Hz, 6H).

Step 2: A mixture of alkyne 18 (1.1 g, 5.0 mmol) and 10% Pd/C (100 mg) in EtOH (20 mL) were shaken under a H_2 atmosphere at 50 psi for 5 hours. The solution was filtered through Celite and concentrated under reduced pressure. The residue was dissolved in EtOH (20 mL), 10% Pd/C (100 mg) was added, and the mixture was shaken again under a H_2 atmosphere at 50 psi for 5 hours. The solution was filtered through Celite and concentrated under reduced pressure to give acetal 19 (900 mg, 84%): $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.68 (d, $J = 3$ Hz,

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1H), 7.19 (d, $J = 3$ Hz, 1H), 4.57 (t, $J = 6$ Hz, 1H), 3.74-3.63 (m, 2H), 3.57-3.45 (m, 2H), 3.11 (t, $J = 7$ Hz, 2H), 2.14 (dt, $J = 14, 6$ Hz, 2H), 1.21 (t, $J = 7$ Hz, 6H).

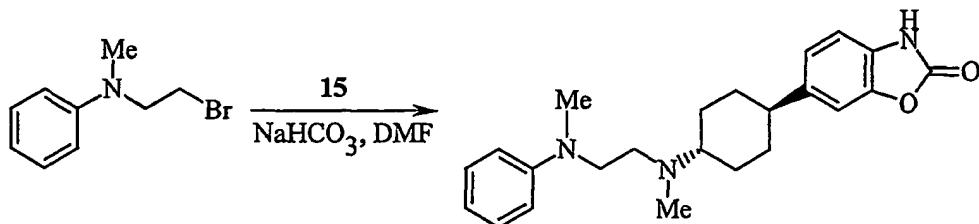
Step 3: To acetal **19** (450 mg, 2.1 mmol) in THF (10 mL) was added *p*-toluenesulfonic acid (20 mg, 0.10 mmol) and H₂O (0.20 mL). The reaction mixture was heated at reflux for 45 minutes, cooled to ambient temperature, and concentrated under reduced pressure. Purification by flash chromatography (silica, 75:25 hexanes:EtOAc) gave aldehyde **20** (200 mg, 30%): ¹H NMR (300 MHz, CDCl₃): δ 9.88 (s, 1H), 7.67 (d, $J = 3$ Hz, 1H), 7.22 (d, $J = 3$ Hz, 1H), 7.22 (d, $J = 3$ Hz, 1H), 3.36 (t, $J = 7$ Hz, 2H), 3.04 (t, $J = 7$ Hz, 2H).

Step 4: Condensation of **15** (200 mg, 1.40 mmol) and aldehyde **20** (340 mg, 1.40 mmol), following the procedure described in Example 45, Step 2, followed by conversion to the HCl salt, gave 6-{*trans*-4-[methyl(3-thiazol-2-ylpropyl)-amino]cyclohexyl}-3*H*-benzoxazol-2-one (311 mg, 50%), as an off-white solid: mp 237-239°C; IR (KBr): 2948, 1767, 1499, 1449 cm⁻¹; ¹H NMR (500 MHz, CD₃OD): δ 8.04 (dd, $J = 4, 1$ Hz, 1H), 7.87 (dd, $J = 4, 1$ Hz, 1H), 7.14 (s, 1H), 7.08-6.99 (m, 2H), 3.53-3.20 (m, 5H), 2.89 (s, 3H), 2.69-2.61 (m, 1H), 2.40-2.26 (m, 2H), 2.24-2.14 (m, 2H), 2.10-2.01 (m, 2H), 1.86-1.61 (m, 4H); APCI (*m/z*): 372 [M + H]⁺; HPLC: method A, 5.34 minutes (>99%); Anal. Calcd for C₂₀H₂₅N₃O₂S·2HCl: C, 54.05; H, 6.12; N, 9.46. Found: C, 53.82; H, 6.21; N, 9.22.

EXAMPLE 60

6-(*trans*-4-{Methyl-[2-(Methylphenylamino)ethyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one

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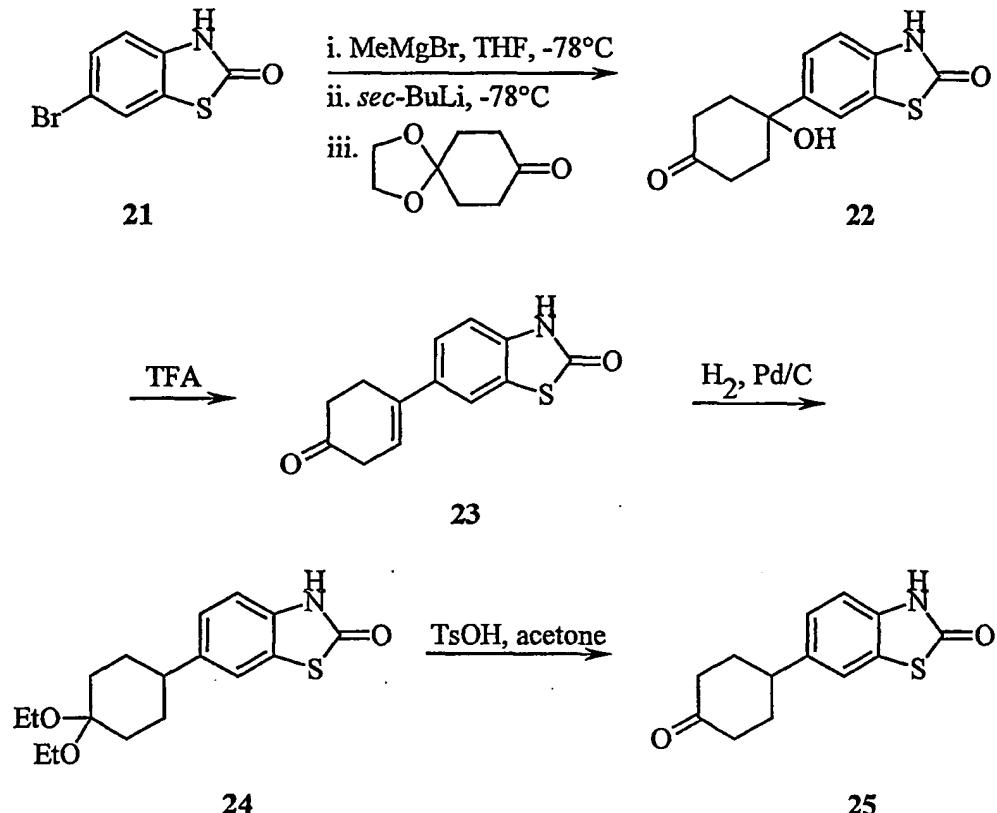


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Step 1: To a solution of amine 2 (780 mg, 3.2 mmol) in DMF (15 mL) was added NaHCO₃ (560 mg, 6.7 mmol) and (2-bromoethyl)methylphenylamine (690 mg, 3.2 mmol). The reaction mixture was gradually heated to 100°C, held at 100°C for 2.5 hours, and then stirred at 50°C for 12 hours. The suspension was cooled to room temperature, diluted with H₂O (35 mL), and extracted with EtOAc (3 × 50 mL). The combined organics were washed with saturated NaCl (50 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 89:10:1 CH₂Cl₂:MeOH:NH₄OH) followed by formation of the HCl salt and recrystallization (MeOH:Et₂O) gave 6-(*trans*-4-{methyl-[2-(methylphenylamino)ethyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one (350 mg, 24%), as a white solid: mp 240-243°C; IR (KBr): 2950, 1765, 1499, 1451 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.72 (br s, 2H), 7.19-7.07 (m, 5H), 6.64 (d, *J* = 8 Hz, 2H), 6.57 (t, *J* = 11 Hz, 1H), 3.97 (t, *J* = 6 Hz, 2H), 3.67 (t, *J* = 6 Hz, 2H), 3.02-2.96 (m, 1H), 2.84 (s, 3H), 2.55 (m, 4H), 2.13 (br d, *J* = 10 Hz, 2H), 1.88 (br d, *J* = 10 Hz, 2H), 1.54-1.42 (m, 4H); HRMS-API (m/z): [M + H]⁺ calcd for C₂₃H₂₉N₃O₂, 380.2338; found, 380.2339; HPLC: method A, 6.37 minutes (93.4%); method B, 11.60 minutes (93.0%); Anal. Calcd for C₂₃H₂₉N₃O₂·2HCl·0.25H₂O: C, 60.46; H, 6.95; N, 9.20. Found: C, 60.65; H, 6.98; N, 9.12.

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Scheme 4

Preparation of 6-(4-Oxocyclohexyl)-3*H*-benzothiazol-2-one 25

Step 1: Bromide **21** (2.88 g, 12.52 mmol) was dissolved in anhydrous THF (50 mL), and the solution was cooled to -78°C . Solutions of MeMgBr (4.59 mL of a 3.0 M solution in Et₂O, 13.77 mmol), sec-BuLi (10.59 mL of a 1.3 M solution in cyclohexane, 13.77 mmol), and 1,4-cyclohexanedione monomethylene ketal (1.95 g, 12.52 mmol) in anhydrous THF (10 mL) were added sequentially at 30-minute intervals. After the final addition, the reaction mixture was allowed to warm to room temperature. The reaction was quenched by the addition of 1N HCl (25 mL). The reaction mixture was diluted with EtOAc (300 mL), washed with saturated NaCl (250 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by silica gel chromatography (eluent 1:1 Hexanes:EtOAc) gave alcohol **22** (1.81 g, 47%), as a white solid: ¹H NMR (500 MHz, CDCl₃): δ 8.48 (br s, 1H), 7.59 (s, 1H), 7.31 (d, *J* = 5 Hz, 1H), 7.04 (d, *J* = 5 Hz, 1H), 2.17-2.04 (m, 4H), 1.81 (d, *J* = 8 Hz, 2H), 1.77 (d, *J* = 8 Hz, 2H).

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Step 2: Alcohol 22 (1.81 g, 5.90 mmol) was stirred in TFA (8 mL) at room temperature for 20 minutes. The red solution was poured into CHCl₃ (200 mL), and the organic layer was washed with H₂O (2 × 100 mL), saturated NaHCO₃ and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give ketone 23 (1.22 g, 85%), as a white solid: ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.42 (s, 1H), 7.34 (d, *J* = 6 Hz, 1H), 7.08 (d, *J* = 6 Hz, 1H), 6.11 (t, *J* = 5 Hz, 1H), 3.04 (d, *J* = 2 Hz, 2H), 2.87 (t, *J* = 7 Hz, 2H), 2.57 (m, 2H).

Step 3: A solution of ketone 23 (1.22 g, 4.98 mmol) and 10% Pd/C (0.25 g) in a 3:2 mixture of EtOAc:EtOH (150 mL) was shaken under a H₂ atmosphere at 50 psi for 4 hours. The solution was filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography (eluent 1.5:1 Hexanes:EtOAc) gave ketal 24 (1.44 g, 98%) as a white solid: ¹H NMR (500 MHz, CD₃OD): δ 7.31 (s, 1H), 7.13 (d, *J* = 6 Hz, 1H), 7.04 (d, *J* = 6 Hz, 1H), 3.53 (q, *J* = 7 Hz, 2H), 3.48 (q, *J* = 7 Hz, 2H), 2.57 (m, 1H), 2.10 (d, *J* = 10 Hz, 2H), 1.76-1.51 (m, 4H), 1.47 (m, 2H), 1.21 (t, *J* = 7 Hz, 3H), 1.18 (t, *J* = 7 Hz, 3H).

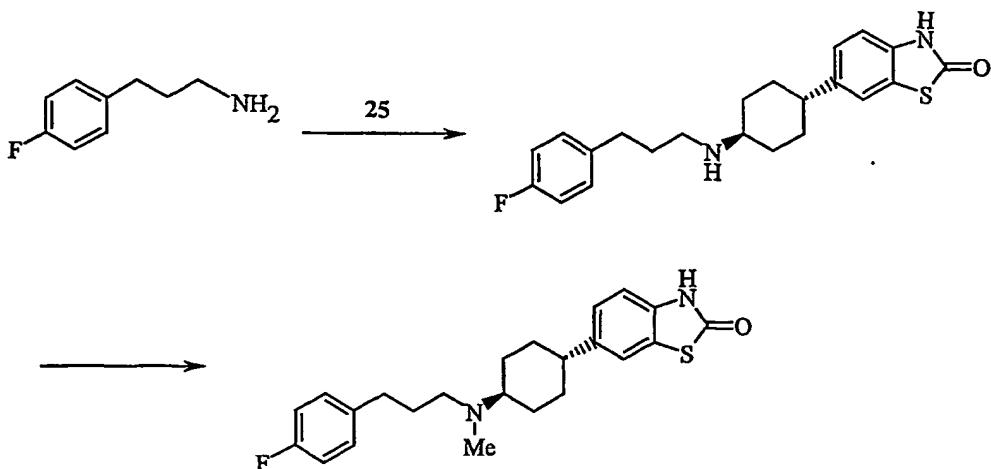
Step 4: Ketal 24 (0.6 g, 1.9 mmol) and TsOH (0.36 g, 1.89 mmol) were stirred in acetone (20 mL) overnight. The reaction mixture was diluted with EtOAc (100 mL) and washed with H₂O (50 mL) and saturated NaHCO₃ (50 mL). The organic layer was concentrated under reduced pressure to give 6-(4-oxocyclohexyl)-3*H*-benzothiazol-2-one 25 (0.48 g, 98%) as a white solid: ¹H NMR (500 MHz, CD₃OD): δ 7.41 (s, 1H), 7.21 (d, *J* = 6 Hz, 1H), 7.06 (d, *J* = 6 Hz, 1H), 3.13 (m, 1H), 2.53 (m, 2H), 2.31 (m, 2H), 2.14 (m, 2H), 1.96 (m, 2H).

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EXAMPLE 61

- (a) 6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzthiazol-2-one
- (b) 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzthiazol-2-one

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Step 1: To a solution of ketone 25 (2.3 g, 9.3 mmol) in 2-propanol

(30 mL) was added 4Å molecular sieves and 3-(4-fluorophenyl)-1-propylamine (1.76 g, 9.3 mmol). The reaction mixture was stirred for 4 hours. Sodium borohydride (0.49 g, 13.03 mmol) was added, and the reaction mixture was stirred overnight, quenched with MeOH, and concentrated under reduced pressure. Purification by flash chromatography (silica, 9.5:5:1 CH₂Cl₂:MeOH:NH₄OH) gave 6-{*trans*-4-[3-(4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzthiazol-2-one (0.24 g, 7%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.39 (s, 1H), 7.25-7.06 (m, 6H), 3.01 (m, 1H), 2.86 (t, *J* = 8 Hz, 2H), 2.61 (t, *J* = 8 Hz, 2H), 2.37 (m, 1H), 2.01 (m, 2H), 1.92-1.81 (m, 4H), 1.49-1.36 (m, 4H).

Step 2: To a stirred solution of 6-{*trans*-4-[3-(4-fluorophenyl)-propylamino]cyclohexyl}-3*H*-benzthiazol-2-one (0.24 g, 0.67 mmol) in MeOH (10 mL) containing H₂O (0.5 mL) was added *p*-formaldehyde (0.1 g, 3.3 mmol).

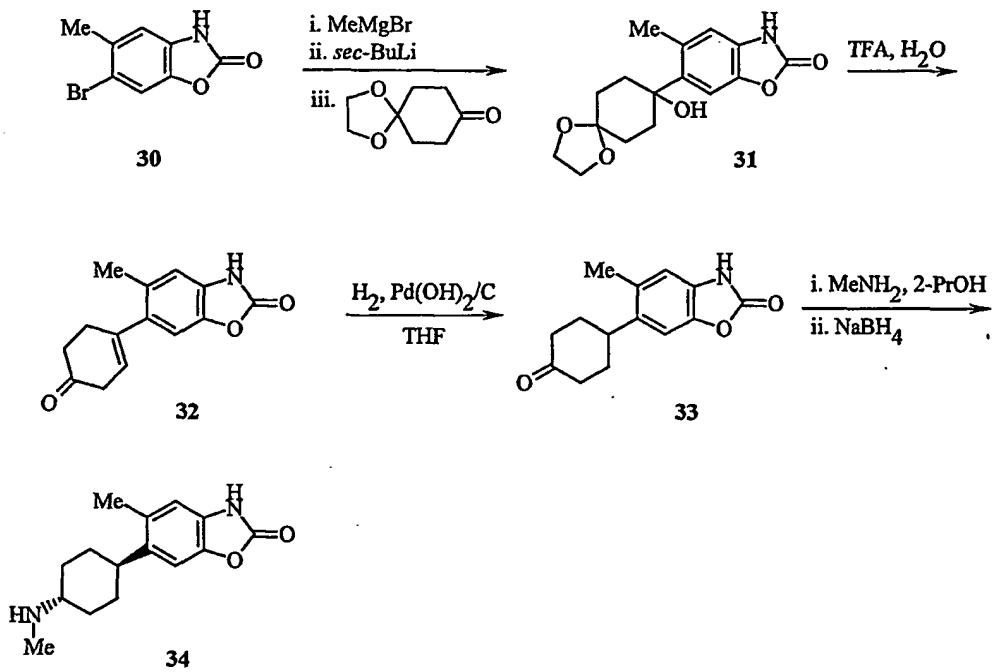
The reaction mixture was stirred for 3 hours. Sodium triacetoxyborohydride (0.2 g, 0.9 mmol) was added, and the mixture was stirred overnight. Solid NaOH was added until the solution became clear. The reaction mixture was concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (eluent 9.5:1:1 CH₂Cl₂:MeOH:NH₄OH) gave 6-(*trans*-4-{[3-(4-fluorophenyl)-propyl]methylamino}cyclohexyl)-3*H*-benzthiazol-2-one (55 mg, 15%), as a pale yellow solid: mp 256-261°C; IR (KBr): 2942, 1683, 1509 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.41 (s, 1H), 7.31-7.03 (m, 6H), 3.29 (m, 2H), 3.01 (m, 2H), 2.70 (s, 3H), 2.64 (m, 2H), 2.11 (m, 1H), 2.08 (m, 1H), 1.99 (m, 2H),

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1.87 (m, 2H), 1.98-1.61 (m, 4H); API-MS (*m/z*): 399 [M + H]⁺; calcd for C₂₃H₂₇FN₂OS, 399.1906; found, 399.1909; HPLC: method A, 5.85 minutes (>99%); method B, 11.48 minutes (>99%); Anal. Calcd for C₂₃H₂₇FN₂OS·HCl·0.75NaCl: C, 57.69; H, 5.89; N, 5.85. Found: C, 57.72; H, 5.96; N, 5.51.

Scheme 5

Preparation of 5-(4-Oxocyclohexyl)-1,3-dihydrobenzimidazol-2-one 29



Step 1: *N*-Bromosuccinimide (112.0 g, 0.63 mol) was added to a stirred solution of 2-hydroxybenzimidazole 26 (84.4 g, 0.63 mol) in glacial acetic acid (930 mL), and the mixture was stirred at room temperature for 12 hours. The reaction mixture was poured into H₂O (3 L), and the yellow solid that formed was collected. Trituration with hot EtOH (1.5 L) gave bromide 27 (113.2 g, 85%), as yellow solid: ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.75 (s, 2H), 7.11-7.05 (m, 2H), 6.87 (d, *J* = 9 Hz, 2H).

Step 2: Bromide 27 (25.0 g, 0.12 mol) was dissolved in anhydrous THF (1.5 L) and the solution was cooled in a -78°C dry ice/2-PrOH bath. A solution of

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MeMgBr (43.0 mL of a 3.0 M solution in Et₂O, 0.13 mol) was added dropwise over 10 minutes, (internal temperature maintained -60°C). After stirring at -78°C for 1 hour, *t*-BuLi (289.4 mL of a 1.7 M solution in pentane, 0.49 mol) was added dropwise over 0.5 hours (again, temperature was maintained below -60°C). After 5 0.75 hours, 1,4-cyclohexanedione mono-ethylene ketal (37.5 g, 0.24 mol) in anhydrous THF (120 mL) was added over 10 minutes. After 0.5 hours, the reaction mixture was warmed to 0°C. The reaction was quenched by the addition of saturated aqueous NH₄Cl (210 mL), and the solution was warmed to room 10 temperature. Most of the THF was removed under reduced pressure, 1N HCl (500 mL) was added, and mixture was extracted with EtOAc (5 × 200 mL). The combined organics were dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue was slurried in EtOAc, and the resulting solid was collected by vacuum filtration and dried (21.4 g). This solid was stirred in TFA (50 mL) at room temperature for 20 minutes. The red solution was poured into CHCl₃ 15 (400 mL) and H₂O (400 mL). A gelatinous solid formed which was collected by vacuum filtration, rinsed with H₂O (150 mL), and dried to give crude 28 (25.5 g, 92%). ¹H NMR (300 MHz, DMSO-*d*₆): δ 10.78 (s, 1H), 10.60 (s, 1H), 7.01-6.85 (m, 3H), 6.05-6.00 (m, 1H), 3.05-3.00 (m, 2H), 2.88-2.79 (m, 2H), 2.59-2.52 (m, 2H).

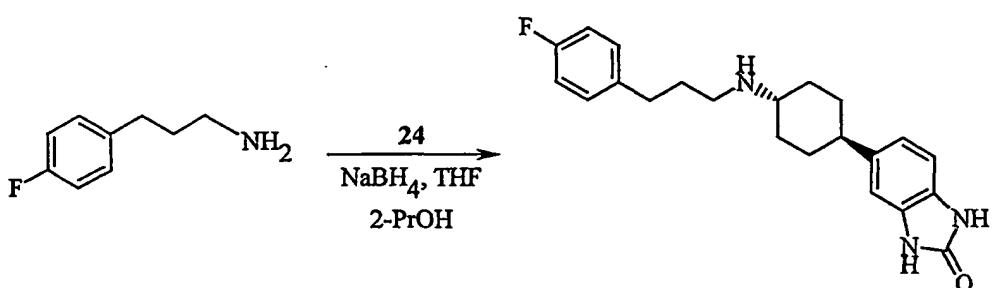
20 Step 3: A mixture of crude 28 (0.85 g, 3.7 mmol) and 10% Pd/C (0.15 g) in EtOH (30 mL) was shaken under a H₂ atmosphere at 50 psi for 3 hours. The solution was filtered through Celite and concentrated under reduced pressure to give crude 5-(4-oxocyclohexyl)-1,3-dihydrobenzoimidazol-2-one 29 (850 mg, 99%): ¹H NMR (300 MHz, DMSO-*d*₆): δ 6.95-6.80 (m, 3H), 3.07-2.95 (m, 1H), 2.67-2.48 (m, 2H), 2.32-2.22 (m, 2H), 2.09-1.97 (m, 2H), 1.90-1.65 (m, 2H).

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EXAMPLE 62

5-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-1,3-dihydrobenzoimidazol-2-one

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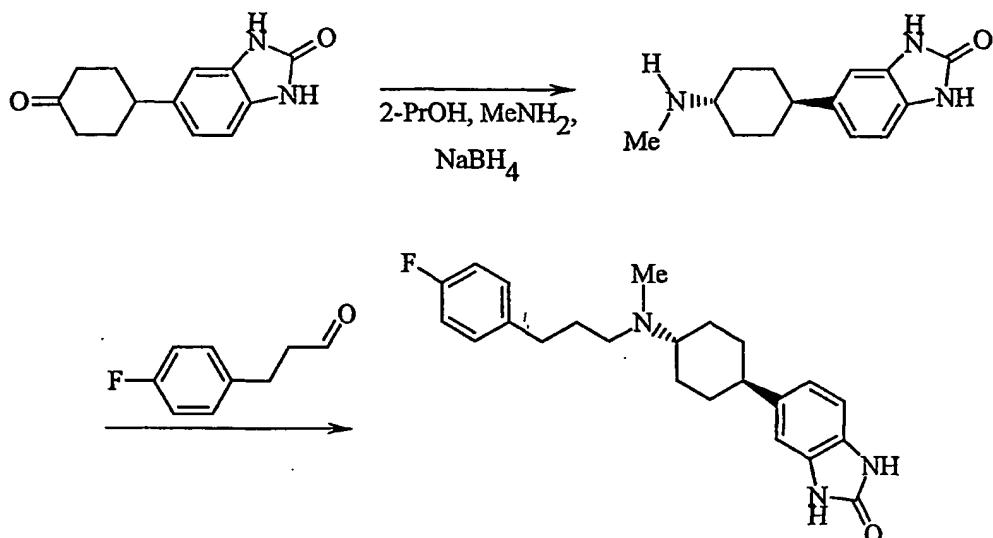


To a solution of (4-fluorophenyl)-1-propylamine (1.9 g, 10.0 mmol) in 2-propanol (90 mL) and THF (25 mL) was added Et₃N (1.5 mL, 11.0 mmol), ketone 24 (2.3 g, 10.0 mmol), and 3Å molecular sieves. The reaction mixture was stirred at room temperature for 3 hours. Sodium borohydride (950 mg, 25.1 mmol) was added, and the reaction mixture was stirred for 12 hours. Additional sodium borohydride (500 mg, 13.2 mmol) was added, and the reaction mixture was stirred for 12 hours. Methanol was added to quench the excess NaBH₄, and the resultant solution was filtered through a pad of Celite and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:10 CH₂Cl₂:MeOH followed by 95:4.5:0.5 CH₂Cl₂:MeOH:NH₄OH), followed by formation of the HCl salt and recrystallization (MeOH:Et₂O), gave 5-{*trans*-4-[3-(4-fluorophenyl)-propylamino]cyclohexyl}-1,3-dihydrobenzoimidazol-2-one (162 mg, 4%), as a white solid: mp 336-339°C; IR (KBr): 2943, 1727, 1686, 1510 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 10.45 (s, 1H), 10.39 (s, 1H), 8.55 (s, 2H), 7.29-7.27 (m, 2H), 7.15-7.12 (m, 2H), 6.83-6.76 (m, 3H), 3.13-3.06 (m, 1H), 2.97-2.89 (m, 2H), 2.68 (t, *J* = 8 Hz, 2H), 2.48-2.44 (m, 1H), 2.15-2.08 (m, 2H), 1.97-1.82 (m, 4H), 1.54-1.43 (m, 4H); API (*m/z*): 368 [M + H]⁺; HPLC: method A, 5.07 minutes (98.8%); method B, 11.00 minutes (98.9%); Anal. Calcd for C₂₂H₂₆FN₃O·HCl·0.25H₂O: C, 64.70; H, 6.79; N, 10.29. Found: C, 64.79; H, 6.74; N, 10.12.

EXAMPLE 63

5-{*trans*-4-[{3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-1,3-dihydrobenzoimidazol-2-one

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Step 1: To a suspension of ketone 29 (2.15 mg, 9.4 mmol) in 2-PrOH (115 mL, HPLC grade) was added methylamine (7.1 mL of a 2.0 M solution in THF, 14.2 mmol). After 1 hour, the reaction mixture was cooled in an ice/water bath and sodium borohydride (530 mg, 14.0 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 12 hours. Methanol (ca 2 mL) was added to quench any excess sodium borohydride, and the solvents were removed under reduced pressure. Purification by flash chromatography (silica, 89:10:1 CH₂Cl₂:MeOH:NH₄OH) followed by formation of the HCl salt and recrystallization (MeOH:Et₂O) gave 5-(4-methylaminocyclohexyl)-1,3-dihydrobenzoimidazol-2-one (402 mg, 13%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 10.58 (s, 1H), 10.51 (s, 1H), 8.81 (s, 2H), 6.99-6.71 (m, 3H), 3.05-2.90 (m, 1H), 2.20-2.09 (m, 2H), 2.48-2.50 (m, 4H), 1.95-1.85 (m, 2H), 1.57-1.39 (m, 4H).

Step 2: To a suspension of 5-(4-methylaminocyclohexyl)-1,3-dihydrobenzoimidazol-2-one (400 mg, 1.4 mmol) in 1:1 CH₂Cl₂:MeOH (32 mL) was added 3-(4-fluorophenyl)propionaldehyde (220 mg, 1.4 mmol) and, after 5 minutes, NaBH(OAc)₃ (420 mg, 2.0 mmol). After 12 hours NaBH(OAc)₃ (300 mg, 1.4 mmol) was added and stirring continued for 8.25 hours. The reaction mixture was brought to pH 8 with solid NaOH and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:4.5:0.5 CH₂Cl₂:MeOH:NH₄OH) and formation of the HCl salt gave 5-(*trans*-4-{[3-(4-fluorophenyl)propyl]methylamino}cyclohexyl)-1,3-

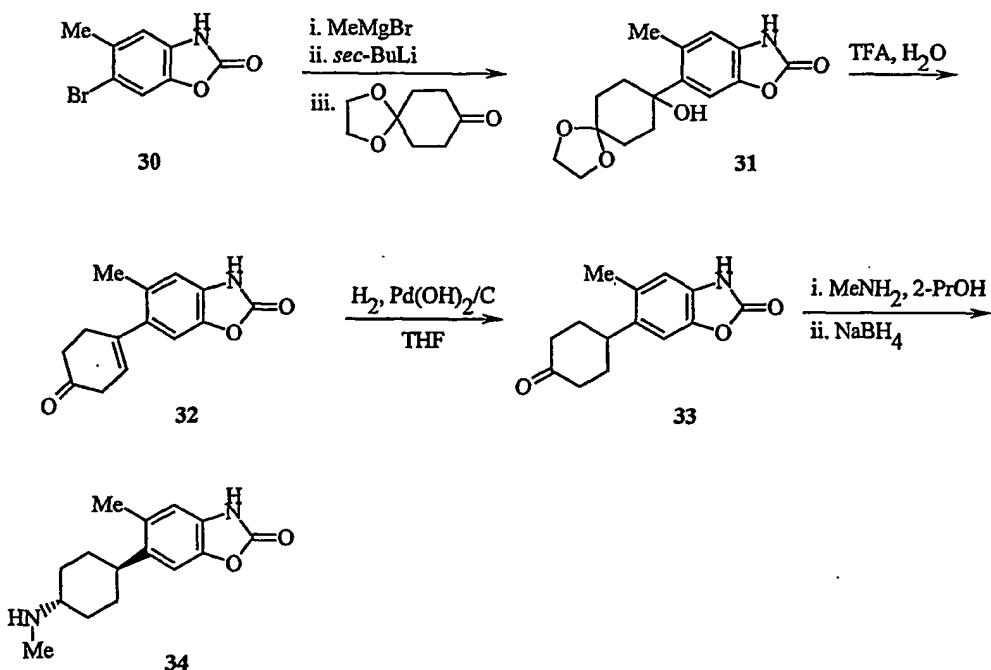
-108-

dihydrobenzoimidazol-2-one (330 mg, 56%), as an off-white foam: IR (KBr): 2949, 1696 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 10.52 (s, 1H), 10.48 (s, 1H), 10.42 (s, 1H), 7.31-7.28 (m, 2H), 7.17-7.11 (m, 2H), 6.87-6.76 (m, 3H), 3.35-3.25 (m, 1H), 3.18-3.09 (m, 1H), 3.02-2.59 (m, 1H), 2.71-2.61 (m, 5H), 2.48-2.45 (m, 1H), 2.19-1.99 (m, 4H), 1.92-1.85 (m, 2H), 1.68-1.49 (m, 4H); ESI (*m/z*): 382 [M + H]⁺; HRMS-API (*m/z*): [M + H]⁺ calcd for C₂₃H₂₈FN₃O, 382.2294; found, 382.2292; method A, 5.64 minutes (>99%); method B, 10.82 minutes (>99%); Anal. Calcd for C₂₃H₂₈FN₃O·HCl·0.75H₂O: C, 64.03; H, 7.13; N, 9.74. Found: C, 63.89; H, 7.22; N, 9.50.

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Scheme 6

Preparation of 5-Methyl-6-(*trans*-4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one **34**



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Step 1: Bromide **30** (5.0 g, 21.9 mmol) was dissolved in anhydrous THF (85 mL), and the solution was cooled to -78°C. Solutions of MeMgBr (8.03 mL of a 3.0 M solution in Et₂O, 24.1 mmol), *sec*-BuLi (18.5 mL of a 1.3 M solution in cyclohexane, 24.1 mmol), and 1,4-cyclohexanedione monoethylene ketal (3.76 g, 24.1 mmol) in anhydrous THF (20 mL) were added sequentially at 30-minute

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intervals. After the final addition, the reaction mixture was allowed to warm to room temperature. The reaction mixture was diluted with EtOAc (500 mL), washed with saturated NaCl (200 mL), and the water layer was extracted with EtOAc (200 mL) and CH₂Cl₂ (200 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated under reduced pressure to provide a crude solid which was purified by flash chromatography (silica, 10% MeOH:CH₂Cl₂) to yield 31 (2.96 g, 44%), as a white solid: ¹H NMR (500 MHz, CDCl₃): δ 8.85 (br s, 1H), 7.38 (s, 1H), 6.83 (s, 1H), 4.03-3.90 (m, 4H), 2.61 (s, 3H), 2.23 (dt, J = 13, 4 Hz, 2H), 2.12 (dt, J = 13, 4 Hz, 2H), 1.96-1.90 (m, 2H), 1.73-1.61 (m, 2H).

Step 2: Compound 31 was stirred in TFA (12 mL) and H₂O (3 mL) and slowly warmed from 0°C to room temperature over 3.5 hours. The red solution was poured into CHCl₃ (300 mL), and the organic layer was washed with H₂O (2 × 100 mL), saturated NaHCO₃, and saturated NaCl, dried (Na₂SO₄), filtered, and concentrated under reduced pressure to give 32 (2.13 g, 91%), as a white solid: ¹H NMR (500 MHz, CD₃OD): δ 6.98 (s, 1H), 6.91 (s, 1H), 5.68 (t, J = 3 Hz, 1H), 3.06-3.02 (m, 2H), 2.73-2.65 (m, 2H), 2.64-2.61 (m, 2H), 2.34 (s, 3H).

Step 3: A mixture of 32 (1.64 g, 6.74 mmol) in THF (100 mL) and 20% Pd(OH)₂/C (490 mg) was shaken under a H₂ atmosphere at 50 psi for 12 hours. The solution was filtered through Celite and concentrated under reduced pressure to give 33 (1.70 g, 100%) as a pale yellow solid: ¹H NMR (500 MHz, CD₃OD): δ 7.11 (s, 1H), 6.90 (s, 1H), 3.36 (tt, J = 13, 3 Hz, 1H), 2.65 (dt, J = 13, 6 Hz, 2H), 2.45-2.39 (m, 5H), 2.15-2.08 (m, 2H), 1.90 (ddd, J = 17, 13, 4 Hz, 2H).

Step 4: Condensation of 33 (1.65 g, 6.74 mmol) with methylamine (5.06 mL, 10.1 mmol) and NaBH₄ (382 mg, 10.1 mmol) in 2-propanol (28 mL), following the procedure described in Example 63, Step 1, gave 5-methyl-6-(*trans*-4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one (34) (207 mg, 12%), as a white solid: ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.08 (s, 1H), 6.82 (s, 1H), 2.63 (tt, J = 12, 3 Hz, 1H), 2.35 (tt, J = 11, 4 Hz, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 1.98 (br d,

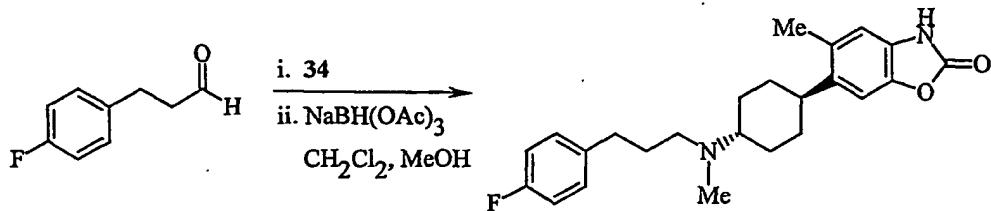
-110-

J = 12 Hz, 2H), 1.68 (br d, *J* = 12 Hz, 2H), 1.44 (ddd, *J* = 16, 13, 3 Hz, 2H),
1.13 (ddd, *J* = 16, 13, 3 Hz, 2H).

EXAMPLE 64

6-(4-{[3-(4-Fluorophenyl)propyl]methyl-amino}cyclohexyl)-5-methyl-3*H*-benzoxazol-2-one

5



Condensation of 5-methyl-6-(*trans*-4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one 34 (0.20 g, 0.77 mmol) with 3-(4-fluorophenyl)-propionaldehyde 25 (0.13 g, 0.85 mmol) and NaBH(OAc)₃ (229 mg, 1.08 mmol)

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in CH₂Cl₂ (4 mL) and MeOH (4 mL), following the procedure described in Example 63, Step 2, gave 6-(4-{[3-(4-fluorophenyl)propyl]methyl-amino}cyclohexyl)-5-methyl-3*H*-benzoxazol-2-one (190 mg, 62%), as a white solid: mp 264-267°C; IR (KBr): 2953, 1765, 1510, 1491 cm⁻¹; ¹H NMR

(500 MHz, DMSO-*d*₆): δ 11.40 (s, 1H), 10.01 (s, 1H), 7.31 (dd, *J* = 8, 6 Hz, 2H), 7.14 (t, *J* = 9 Hz, 2H), 7.11 (s, 1H), 6.88 (s, 1H), 3.35-3.28 (m, 1H), 3.19-3.12 (m, 1H), 3.05-2.98 (m, 1H), 2.72 (d, *J* = 5 Hz, 3H), 2.69-2.62 (m, 2H), 2.53-2.46 (m, 1H), 2.29 (s, 3H), 2.14-1.97 (m, 4H), 1.85-1.78 (m, 2H), 1.72-1.50 (m, 4H); ESI (*m/z*): 397 [M + H]⁺; HPLC: method A, 6.37 minutes (>99%); Anal. Calcd for C₂₄H₂₉FN₂O₂·HCl: C, 66.58; H, 6.98; N, 6.47. Found: C, 66.47; H, 7.02; N,

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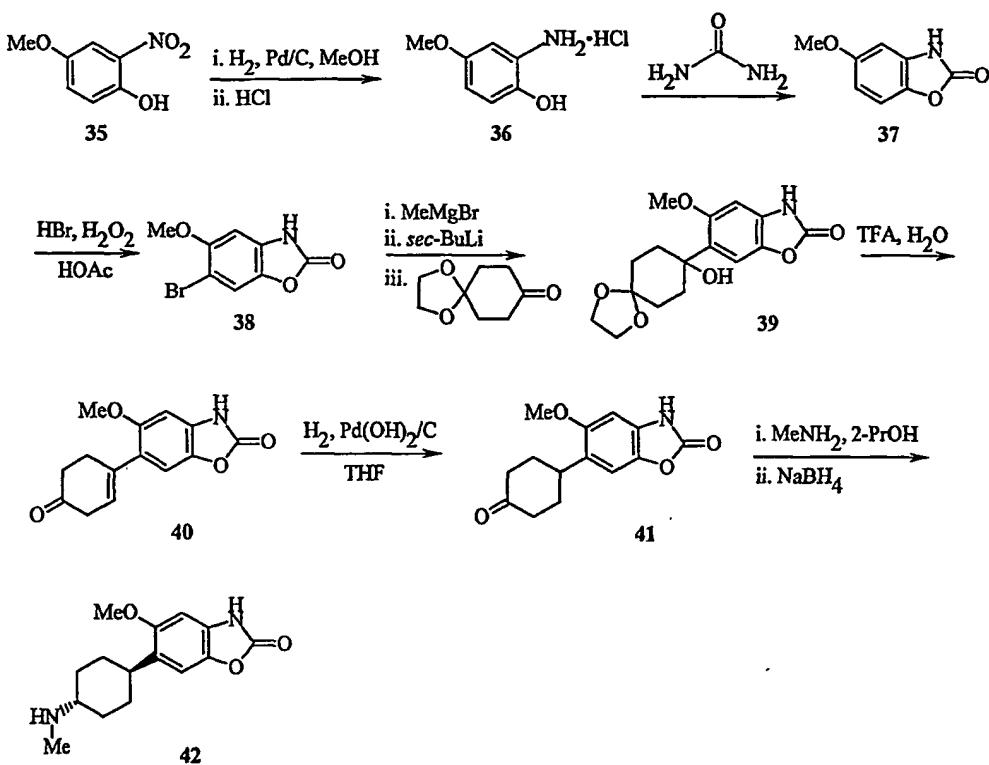
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Scheme 7

Preparation of 5-Methoxy-6-(4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one 42

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Step 1: To a solution of 4-methoxy-2-nitrophenol 35 (10.0 g, 59.1 mmol) in MeOH (500 mL) was added 10% Pd/C (1.0 g), and the reaction was stirred under a H₂ atmosphere at balloon pressure for 4 hours. The reaction was acidified with HCl (60 mL of a 1N solution in Et₂O, 60 mmol), and then filtered through Celite. Concentration under reduced pressure gave 36 (10.4 g, 100%), which was used without further purification: ¹H NMR (500 MHz, CD₃OD): δ 6.96-6.87 (m, 3H), 3.75 (s, 3H).

Step 2: A mixture of salt 36 (10.3 g, 58.7 mmol) and urea (5.64 g, 93.9 mmol) was heated at 180°C for 2 hours. After the reaction was cooled to room temperature, 1N HCl was added, and the water layer was extracted with EtOAc. The organic layer was dried (Na₂SO₄) and filtered. Concentration under reduced pressure gave 37 (7.46 g, 77%), which was used without further purification: ¹H NMR (300 MHz, CD₃OD): δ 7.14-7.06 (m, 1H), 6.68-6.62 (m, 2H), 3.78 (s, 3H).

Step 3: To a solution of 37 (8.27 g, 50.1 mmol) in HOAc (30 mL) were added hydrogen bromide (22.9 mL, 115 mmol) and hydrogen peroxide (6.55 mL,

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64.1 mmol) at 10°C. The reaction was allowed to warm to room temperature and then stirred 1 hour. Water (50 mL) was added to the reaction mixture. The dark gray solid which formed was collected by filtration, and then washed with H₂O (50 mL). The crude solid was dissolved in hot EtOH, and hexane was added until a precipitate formed. The precipitate was collected by filtration to 38 (9.44 g, 77%): ¹H NMR (300 MHz, CD₃OD): δ 7.42 (s, 1H), 6.83 (s, 1H), 3.84 (s, 3H).

Step 4: Condensation of 38 (3.36 g, 13.8 mmol) with 1,4-cyclohexanedione monoethylene ketal (2.37 g, 15.2 mmol), following the procedure described in Step 2, Scheme 2, gave 39 (3.12 g, 70%), as a brown foam: ¹H NMR (500 MHz, CDCl₃): δ 9.80 (br s, 1H), 7.22 (s, 1H), 6.74 (s, 1H), 4.02-3.93 (m, 4H), 3.92 (s, 3H), 3.49 (s, 1H), 2.22-2.13 (m, 2H), 2.09-2.05 (m, 4H), 1.70-1.65 (m, 2H).

Step 5: The reaction of 39 (3.12 g, 9.71 mmol) in TFA (12 mL) and H₂O (3 mL), following the procedure described in Step 3, Scheme 2, gave 40 (2.50 g, 99%) as a pale yellow solid: ¹H NMR (500 MHz, CD₃OD): δ 7.04 (s, 1H), 6.75 (s, 1H), 5.78 (t, *J* = 3 Hz, 1H), 3.83 (s, 3H), 3.06-3.02 (m, 2H), 2.80-2.75 (m, 2H), 2.58 (t, *J* = 7 Hz, 2H).

Step 6: A mixture of 40 (2.50 g, 9.64 mmol) in THF (150 mL) and 20% Pd(OH)₂/C (700 mg) was shaken under a H₂ atmosphere at 50 psi for 12 hours. The solution was filtered through Celite and concentrated under reduced pressure to give 41 (1.56 g, 62%), as a mustard-colored solid: ¹H NMR (500 MHz, CD₃OD): δ 7.10 (s, 1H), 6.77 (s, 1H), 3.86 (s, 3H), 3.52 (tt, *J* = 9, 3 Hz, 1H), 2.60 (ddd, *J* = 14, 14, 6 Hz, 2H), 2.40 (dt, *J* = 15, 2 Hz, 2H), 2.15-2.08 (m, 2H), 1.91-1.85 (m, 2H).

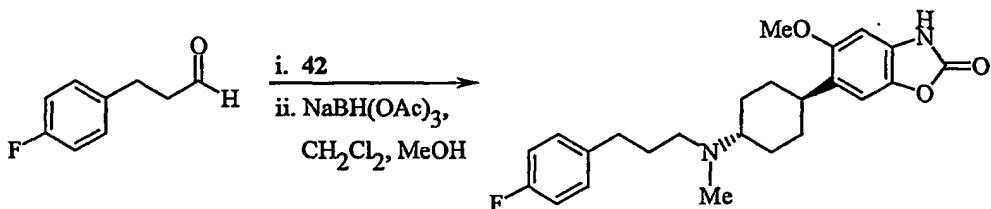
Step 7: Condensation of 41 (2.49 g, 9.53 mmol) with methylamine (7.2 mL, 14.3 mmol) and NaBH₄ (541 mg, 14.3 mmol) in 2-propanol (40 mL), following the procedure described in Example 63, Step 1, gave 5-methoxy-6-(4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one 42 (200 mg, 12%), as a white solid: ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.05 (s, 1H), 6.67 (s, 1H), 3.78 (s, 3H),

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2.83 (tt, $J = 9, 3$ Hz, 1H), 2.36-2.31 (m, 1H), 2.30 (s, 3H), 1.98 (br d, $J = 12$ Hz, 2H), 1.70 (br d, $J = 12$ Hz, 2H), 1.47-1.35 (m, 2H), 1.15-1.05 (m, 2H).

EXAMPLE 65

5 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-5-methoxy-3*H*-benzoxazol-2-one

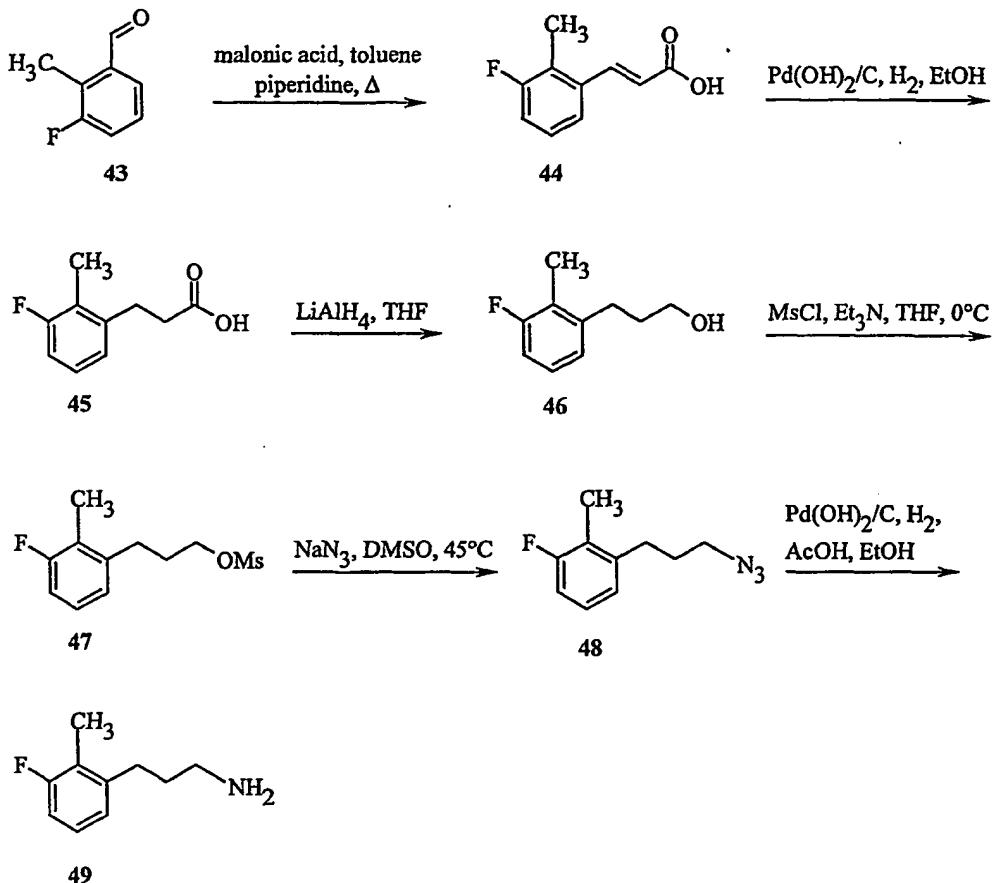


Condensation of 5-methoxy-6-(4-methylaminocyclohexyl)-3*H*-benzoxazol-2-one 42 (0.20 g, 0.72 mmol) with 3-(4-fluorophenyl)-propionaldehyde 25 (0.12 g, 0.79 mmol) and NaBH(OAc)₃ (214 mg, 1.01 mmol) in CH₂Cl₂ (4 mL) and MeOH (4 mL), following the procedure described in Example 63, Step 2, gave 6-(*trans*-4-{[3-(4-fluorophenyl)propyl]methylamino}-cyclohexyl)-5-methoxy-3*H*-benzoxazol-2-one (236 mg, 79%), as an off-white solid: mp 239-242°C; IR (KBr): 3435, 2945, 1767, 1510, 1495 cm⁻¹; ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.50 (s, 1H), 10.35 (br s, 1H), 7.29 (dd, $J = 9, 6$ Hz, 2H), 7.13 (t, $J = 9$ Hz, 2H), 7.08 (s, 1H), 6.72 (s, 1H), 3.35-3.30 (m, 1H), 3.28 (s, 3H), 3.19-3.12 (m, 1H), 3.02-2.95 (m, 1H), 2.90 (tt, $J = 12, 9$ Hz, 3H), 2.68 (d, $J = 5$ Hz, 3H), 2.68-2.62 (m, 2H), 2.15-1.95 (m, 4H), 1.85-1.77 (m, 2H), 1.69-1.45 (m, 4H); ESI (*m/z*): 413 [M + H]⁺; HPLC: method A, 6.31 minutes (>99%), method B, 11.6 minutes (>99%); Anal. Calcd for C₂₄H₂₉FN₂O₃·HCl·H₂O: C, 61.73; H, 6.91; N, 6.00. Found: C, 61.85; H, 6.96; N, 5.87.

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Scheme 8

General Procedure for the Preparation of Aryl Amines and Aldehydes



Step 1: A mixture of 3-fluoro-2-methylbenzaldehyde (10 g, 72 mmol),
 5 malonic acid (8.3 g, 80 mmol), piperidine (0.35 mL, 3.6 mmol), and toluene
 (150 mL) was heated to reflux (flask equipped with a Dean-stark trap) for
 22 hours. After cooling to ambient temperature, the reaction mixture was
 extracted with saturated NaHCO_3 (2×30 mL), brought to pH 3 with 1N HCl, and
 extracted with EtOAc (3×50 mL). The combined organic extracts were dried
 10 (Na_2SO_4), filtered, and concentrated under reduced pressure to give cinnamic
 acid 44 (5.2 g, 40%) which was used without further purification: $^1\text{H NMR}$
 (500 MHz, $\text{DMSO}-d_6$): δ 12.48 (s, 1H), 7.79 (d, $J = 16$ Hz, 1H), 7.53 (d,
 $J = 8$ Hz, 1H), 7.26 (dd, $J = 8, 8$ Hz, 1H), 7.19 (dd, $J = 8, 8$ Hz, 1H), 6.45 (d,
 $J = 16$ Hz, 1H), 2.26 (s, 3H).

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Step 2: A mixture of cinnamic acid 44 (5.2 g, 29 mmol) and 20% Pd(OH)₂/C (100 mg) in EtOH (150 mL) was shaken under a H₂ atmosphere (balloon) for 22 hours. The solution was filtered through Celite and concentrated under reduced pressure to give acid 45 (5.2 g, 100%), which was used without further purification: ¹H NMR (500 MHz, DMSO-*d*₆): δ 12.15 (s, 1H), 7.14 (dd, *J* = 8, 8 Hz, 1H), 7.00 (d, *J* = 8 Hz, 1H), 6.97 (dd, *J* = 8, 8 Hz, 1H), 2.84 (dd, *J* = 8, 7 Hz, 2H), 2.48 (dd, *J* = 8, 7 Hz, 2H), 2.17 (d, *J* = 2 Hz, 3H).

Step 3: To an ice-cold, stirred solution of acid 45 (5.1 g, 28 mmol) in THF (50 mL) was added LiAlH₄ (1.1 g, 28 mmol) portionwise over 10 minutes. After stirring for 1 hour, the reaction mixture was carefully quenched with methanol, diluted with EtOAc, filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue was taken up in EtOAc, washed with 1N HCl, H₂O, saturated NaCl, dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 95:5 methylene chloride/methanol) gave alcohol 46 (4.8 g, 100%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.14 (dd, *J* = 8, 8 Hz, 1H), 7.00-6.92 (m, 2H), 4.44 (dd, *J* = 7, 7 Hz, 1H), 3.54-3.41 (m, 2H), 2.66 (dd, *J* = 8, 8 Hz, 2H), 2.16 (s, 3H), 1.67-1.62 (m, 2H).

Step 4: To an ice-cold, stirred solution of alcohol 46 (4.8 g, 29 mmol) in THF (150 mL) was added Et₃N (5.8 mL, 42 mmol) and then methanesulfonyl chloride (2.7 mL, 34 mmol). The reaction mixture was stirred for 10 minutes and then diluted with EtOAc (300 mL). The organic layer was washed with 1N HCl (100 mL), H₂O (100 mL), saturated NaHCO₃ (100 mL), saturated NaCl (100 mL), dried (Na₂SO₄), and filtered. Concentration under reduced pressure gave the desired mesylate 47 (7.5 g, 100%) which was used without further purification: ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.14 (dd, *J* = 8, 8 Hz, 1H), 7.02-6.95 (m, 2H), 4.23 (dd, *J* = 7, 6 Hz, 2H), 3.17 (s, 3H), 2.70 (dd, *J* = 8, 7 Hz, 2H), 2.17 (s, 3H), 1.94-1.88 (m, 2H).

Step 5: A mixture of mesylate 47 (7.1 g, 29 mmol), NaN₃ (2.8 g, 43 mmol), and tetrabutylammonium hydrogen sulfate (0.98 g, 2.9 mmol) in DMSO (50 mL) was heated to 45°C for 16 hours. After cooling, the reaction

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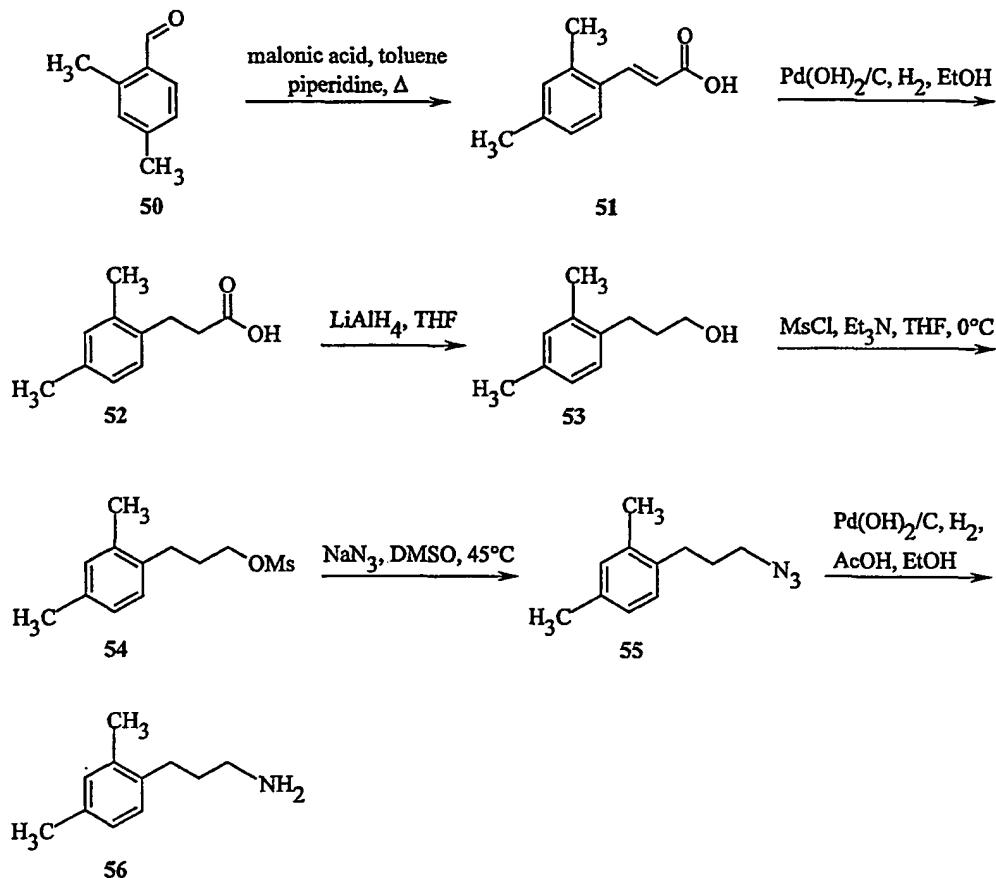
mixture was diluted with EtOAc (300 mL) and washed with H₂O (3 × 100 mL), saturated NaCl (100 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash chromatography (silica, 90:10 hexanes:EtOAc) gave azide 48 (3.9 g, 70%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.15 (dd, *J* = 8, 8 Hz, 1H), 7.00-6.96 (m, 2H), 3.37 (dd, *J* = 8, 7 Hz, 2H), 2.66 (dd, *J* = 8, 7 Hz, 2H), 2.17 (s, 3H), 1.79-1.73 (m, 2H).

Step 6: A mixture of azide 48 (3.9 g, 20 mmol), acetic acid (1.1 mL, 20 mmol), and 20% Pd(OH)₂/C (150 mg) in EtOH (60 mL) was shaken under a H₂ atmosphere (balloon) for 30 hours. The solution was filtered through Celite and concentrated under reduced pressure. The residue was triturated with Et₂O, and the resulting solid was collected by filtration to afford 3-(2-methyl-3-fluorophenyl)-1-propylamine 49 (2.3 g, 51%), as the AcOH salt: ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.14 (dd, *J* = 8, 8 Hz, 1H), 7.00-6.94 (m, 2H), 6.20 (br s, 3H), 2.67-2.62 (m, 4H), 2.16 (d, *J* = 2 Hz, 3H), 1.78 (s, 3H), 1.69-1.63 (m, 2H).

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Scheme 9

Preparation of 3-(2,4-Dimethylphenyl)-1-propylamine 56



Step 1: Reaction of 2,4-dimethylbenzaldehyde (10 g, 75 mmol), malonic acid (8.5 g, 82 mmol), piperidine (0.37 mL, 3.7 mmol), and toluene (150 mL), following the procedure described in the General Procedure, Scheme 8, Step 1, gave cinnamic acid 51 (6.5 g, 49%): ¹H NMR (500 MHz, CD₃OD): δ 7.96 (d, *J* = 16 Hz, 1H), 7.50 (d, *J* = 8 Hz, 1H), 7.04-7.01 (m, 2H), 6.33 (d, *J* = 16 Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H).

Step 2: Hydrogenation of cinnamic acid 51 (6.5 g, 37 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, gave acid 52 (6.6 g, 100%): ¹H NMR (500 MHz, CD₃OD): δ 7.03-6.88 (m, 3H), 2.86 (dd, *J* = 8, 8 Hz, 2H), 2.51 (dd, *J* = 8, 8 Hz, 2H), 2.26 (s, 3H), 2.23 (s, 3H).

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Step 3: Reduction of acid 52 (6.6 g, 38 mmol) with LiAlH₄ (1.4 g, 38 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol 53 (6.3 g, 100%): ¹H NMR (500 MHz, CD₃OD): δ 7.00-6.86 (m, 3H), 3.57 (dd, *J* = 7, 7 Hz, 2H), 2.61 (dd, *J* = 8, 8 Hz, 2H), 2.25 (s, 3H), 5 2.23 (s, 3H), 1.79-1.69 (m, 2H).

Step 4: Reaction of alcohol 53 (6.3 g, 38 mmol) with methanesulfonyl chloride (3.5 mL, 46 mmol), following the procedure described in the General Procedure, Scheme 8, Step 4, gave mesylate 54 (8.6 g, 93%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.01-6.90 (m, 3H), 4.23 (dd, *J* = 8, 8 Hz, 2H), 3.04 (s, 3H), 10 2.69 (dd, *J* = 8, 8 Hz, 2H), 2.26 (s, 3H), 2.24 (s, 3H), 2.00-1.95 (m, 2H).

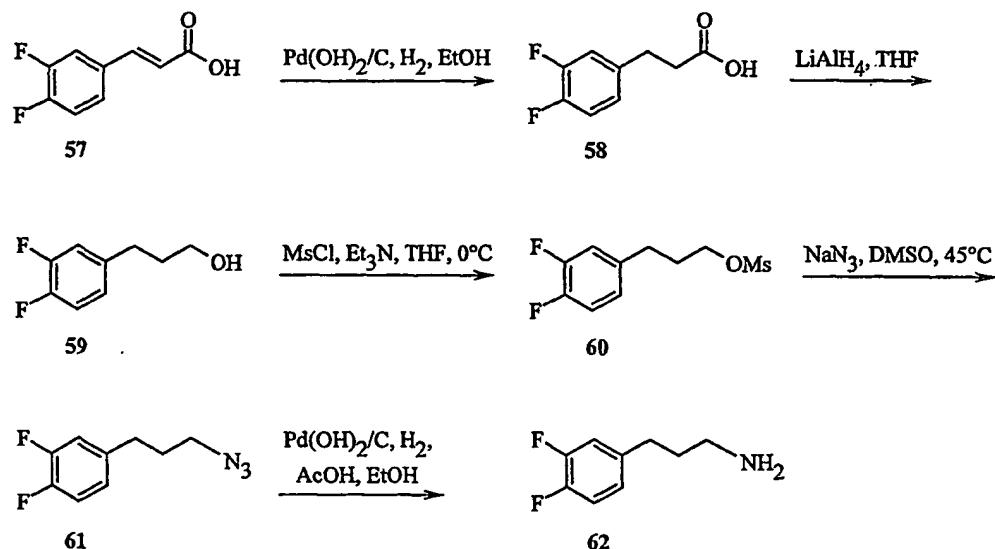
Step 5: Reaction of mesylate 54 (8.6 g, 35 mmol) with NaN₃ (2.8 g, 43 mmol) in DMSO (40 mL), following the procedure described in the General Procedure, Scheme 8, Step 5, gave azide 55 (6.3 g, 95%): ¹H NMR (500 MHz, CD₃OD): δ 6.98-6.89 (m, 3H), 3.31-3.28 (m, 2H), 2.64 (dd, *J* = 8, 8 Hz, 2H), 15 2.25 (s, 3H), 2.24 (s, 3H), 1.81-1.78 (m, 2H).

Step 6: Hydrogenation of azide 55 (3.4 g, 18 mmol), following the procedure described in the General Procedure, Scheme 8, Step 6, gave 3-(2,4-dimethylphenyl)-1-propylamine 56 (1.9 g, 47%), as the AcOH salt: ¹H NMR (500 MHz, CD₃OD): δ 7.01 (d, *J* = 8 Hz, 1H), 6.96 (s, 1H), 6.82 (d, *J* = 8 Hz, 20 1H), 2.95-2.91 (m, 2H), 2.66 (dd, *J* = 8, 8 Hz, 2H), 2.27 (s, 3H), 2.24 (s, 3H), 1.88 (s, 3H), 1.89-1.87 (m, 2H).

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Scheme 10

Preparation of 3-(3,4-Difluorophenyl)-1-propylamine 62



Step 1: Hydrogenation of cinnamic acid 57 (5.0 g, 27 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, gave acid 58 (5.0 g, 100%): ¹H NMR (500 MHz, CD₃OD): δ 7.15-7.09 (m, 2H), 7.01-6.99 (m, 1H), 2.88 (dd, *J* = 8, 8 Hz, 2H), 2.58 (dd, *J* = 8, 8 Hz, 2H).

Step 2: Reduction of acid 58 (5.0 g, 27 mmol) with LiAlH₄ (1.1 g, 29 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol 59 (3.2 g, 70%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.35-7.22 (m, 2H), 7.05-7.01 (m, 1H), 4.50 (br s, 1H), 3.39 (dd, *J* = 7, 7 Hz, 2H), 2.60 (dd, *J* = 8, 8 Hz, 2H), 1.74-1.64 (m, 2H).

Step 3: Reaction of alcohol 59 (8.1 g, 47 mmol) with methanesulfonyl chloride (4.4 mL, 56 mmol), following the procedure described in the General Procedure, Scheme 8, Step 4, gave mesylate 60 (11.5 g, 98%): ¹H NMR (500 MHz, CD₃OD): δ 7.16-7.10 (m, 2H), 7.02-6.99 (m, 1H), 4.22 (dd, *J* = 8, 8 Hz, 2H), 3.04 (s, 3H), 2.72 (dd, *J* = 8, 8 Hz, 2H), 2.05-1.99 (m, 2H).

Step 4: Reaction of mesylate 60 (12 g, 50 mmol) with NaN₃ (3.6 g, 55 mmol) in DMSO (60 mL), following the procedure described in the General Procedure, Scheme 8, Step 5, gave azide 61 (8.8 g, 89%): ¹H NMR (500 MHz,

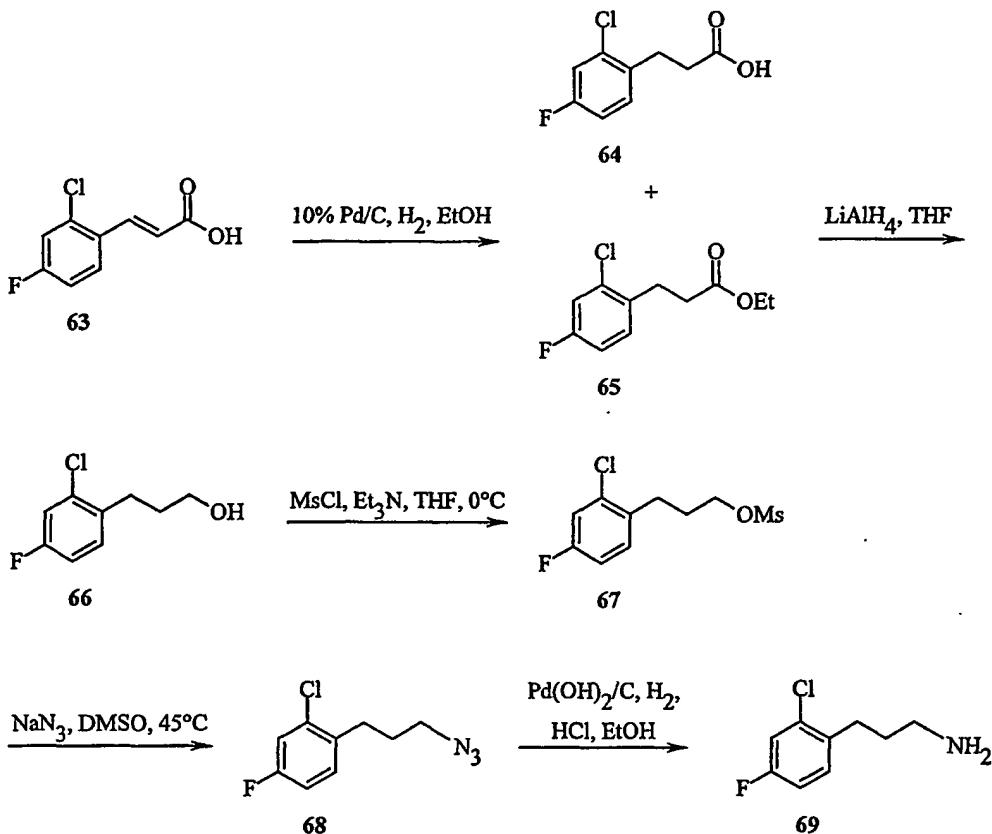
-120-

CD_3OD): δ 7.16-7.09 (m, 2H), 7.02-6.99 (m, 1H), 3.29 (dd, $J = 8, 8$ Hz, 2H), 2.67 (dd, $J = 8, 8$ Hz, 2H), 1.90-1.81 (m, 2H).

Step 5: Hydrogenation of azide 61 (8.8 g, 45 mmol), following the procedure described in the General Procedure, Scheme 8, Step 6, gave 3-(3,4-difluorophenyl)-1-propylamine 62 (1.9 g, 47%), which was converted to the HCl salt: ^1H NMR (500 MHz, $\text{DMSO}-d_6$): δ 8.09 (br s, 3H), 7.37-7.29 (m, 2H), 7.09-7.06 (m, 1H), 2.75-2.72 (m, 2H), 2.66 (dd, $J = 8, 8$ Hz, 2H), 1.89-1.83 (m, 2H).

Scheme 11

Preparation of 3-(2-Chloro-4-fluorophenyl)-1-propylamine 69



Step 1: Hydrogenation of cinnamic acid 63 (10 g, 52 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, except 10% Pd/C was used as catalyst, gave a mixture of acid 64 and ethyl ester 65 (11 g). Reduction of the mixture with LiAlH_4 (1.8 g, 48 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol 66 (9.7 g,

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100%): ^1H NMR (500 MHz, CD₃OD): δ 7.30 (dd, $J = 9, 7$ Hz, 1H), 7.20-7.14 (m, 1H), 7.00-6.96 (m, 1H), 3.58 (dd, $J = 7, 7$ Hz, 2H), 2.78 (dd, $J = 7, 7$ Hz, 2H), 1.84-1.78 (m, 2H).

Step 2: Reaction of alcohol 66 (9.1 g, 48 mmol) with methanesulfonyl chloride (4.5 mL, 58 mmol), following the procedure described in the General Procedure, Scheme 8, Step 4, gave mesylate 67 (13 g, 100%): ^1H NMR (500 MHz, CD₃OD): δ 7.34 (dd, $J = 7, 7$ Hz, 1H), 7.19 (dd, $J = 9, 3$ Hz, 1H), 7.02 (ddd, $J = 9, 7, 3$ Hz, 1H), 4.26 (dd, $J = 7, 7$ Hz, 2H), 3.06 (s, 3H), 2.86 (dd, $J = 8, 8$ Hz, 2H), 2.06-2.01 (m, 2H).

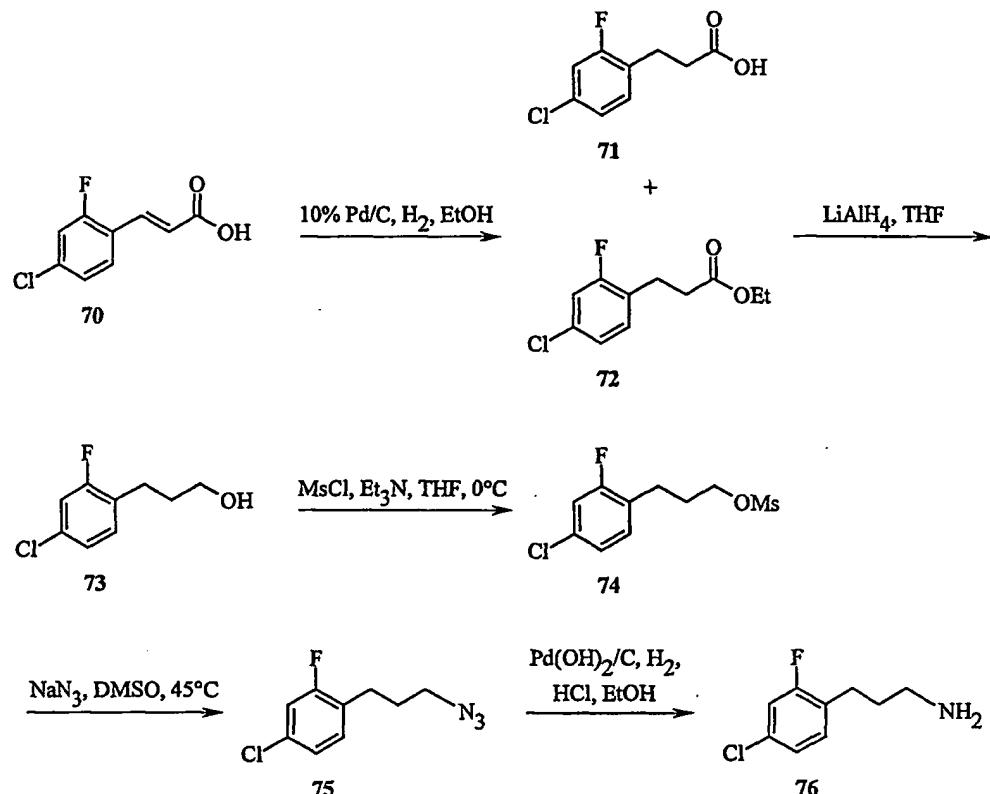
Step 3: Reaction of mesylate 67 (13 g, 49 mmol) with NaN₃ (3.4 g, 53 mmol) in DMSO (50 mL), following the procedure described in the General Procedure, Scheme 8, Step 5, gave azide 68 (9.9 g, 96%): ^1H NMR (500 MHz, CD₃OD): δ 7.32-7.28 (m, 1H), 7.21-7.16 (m, 1H), 7.02-6.97 (m, 1H), 3.33 (dd, $J = 8, 8$ Hz, 2H), 2.82-2.79 (m, 2H), 1.90-1.83 (m, 2H).

Step 4: Hydrogenation of azide 68 (10 g, 48 mmol), following the procedure described in the General Procedure, Scheme 8, Step 6, except HCl was used in place of AcOH, gave 3-(2-chloro-4-fluorophenyl)-1-propylamine 69 (7.8 g, 72%), as the HCl salt: ^1H NMR (500 MHz, DMSO-*d*₆): δ 8.20 (br s, 3H), 7.45 (dd, $J = 7, 7$ Hz, 1H), 7.40 (dd, $J = 9, 3$ Hz, 1H), 7.19 (ddd, $J = 9, 7, 3$ Hz, 1H), 2.84-2.74 (m, 4H), 1.91-1.84 (m, 2H).

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Scheme 12

Preparation of 3-(4-Chloro-2-fluorophenyl)-1-propylamine 76



Step 1: Hydrogenation of cinnamic acid 70 (12 g, 60 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, except Pd/C was used, gave a mixture of acid 71 and ethyl ester 72 (12 g). Reduction of the mixture with LiAlH₄ (1.9 g, 50 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol 73 (9.4 g, 100%): ¹H NMR (500 MHz, CD₃OD): δ 7.26-7.22 (m, 1H), 7.12-7.09 (m, 2H), 3.57 (dd, *J* = 7, 7 Hz, 2H), 2.70 (dd, *J* = 7, 7 Hz, 2H), 1.84-1.77 (m, 2H).

Step 2: Reaction of alcohol 73 (9.4 g, 50 mmol) with methanesulfonyl chloride (4.6 mL, 60 mmol), following the procedure described in the General Procedure, Scheme 8, Step 4, gave mesylate 74 (13 g, 100%): ¹H NMR (500 MHz, CD₃OD): δ 7.28 (dd, *J* = 7, 7 Hz, 1H), 7.15-7.13 (m, 2H), 4.24 (dd, *J* = 7, 7 Hz, 2H), 3.06 (s, 3H), 2.77 (dd, *J* = 8, 8 Hz, 2H), 2.06-2.00 (m, 2H).

Step 3: Reaction of mesylate 74 (13 g, 50 mmol) with NaN₃ (3.6 g, 55 mmol) in DMSO (50 mL), following the procedure described in the General

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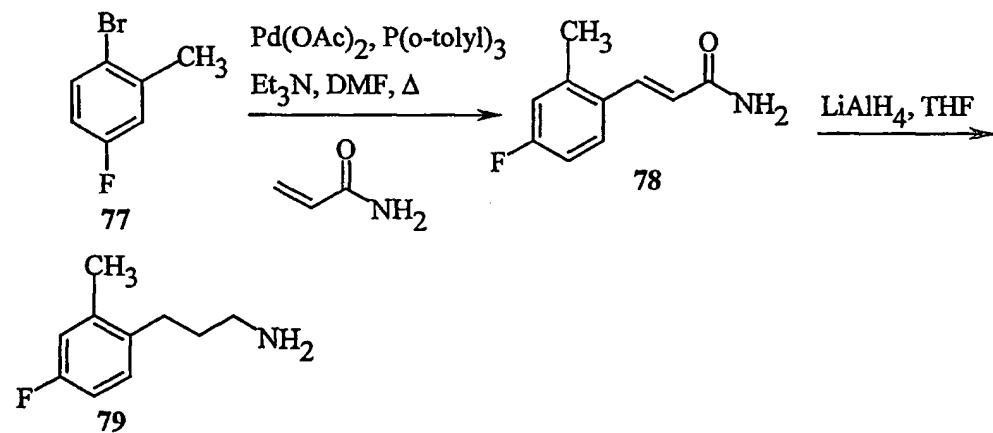
Procedure, Scheme 8, Step 5, gave azide 75 (11 g, 96%): ^1H NMR (500 MHz, CD₃OD): δ 7.26-7.22 (m, 1H), 7.14-7.09 (m, 2H), 3.31 (dd, J = 7, 7 Hz, 2H), 2.70 (dd, J = 7, 7 Hz, 2H), 1.90-1.83 (m, 2H).

Step 4: Hydrogenation of azide 75 (11 g, 50 mmol), following the procedure described in the General Procedure, Scheme 8, Step 6, except HCl was used in place of AcOH, gave 3-(4-chloro-2-fluorophenyl)-1-propylamine 76 (7.4 g, 66%), as the HCl salt: ^1H NMR (500 MHz, DMSO-*d*₆): δ 8.18 (br s, 3H), 7.41-7.36 (m, 2H), 7.26-7.31 (m, 1H), 2.84-2.77 (m, 2H), 2.69 (dd, J = 8, 8 Hz, 2H), 1.90-1.83 (m, 2H).

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Scheme 13

Preparation of 3-(4-Fluoro-2-methylphenyl)-1-propylamine 79



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Step 1: A mixture of 2-bromo-5-fluorotoluene (2.0 g, 11 mmol), acrylamide (1.5 g, 21 mmol), $\text{P}(\text{o-tolyl})_3$ (320 mg, 1.1 mmol), and Et_3N (2.9 mL, 21 mmol), in toluene (25 mL) was deoxygenated by bubbling a stream of Ar through the solution for 15 minutes. Palladium(II) acetate (120 mg, 0.53 mmol) was added to the reaction mixture, and a stream of Ar was again passed through the mixture for 15 minutes. The reaction was heated to 140°C for 2.25 hours, then cooled to ambient temperature, diluted with EtOAc , and filtered through Celite. The filtrate was washed with H_2O , 1N HCl, H_2O , dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give amide 78 (1.7 g, 86%) which was used without further purification: ^1H NMR (500 MHz, DMSO-*d*₆): δ 7.60-7.52 (m, 3H), 7.15-7.04 (m, 3H), 6.46 (d, J = 16 Hz, 1H), 2.37 (s, 3H).

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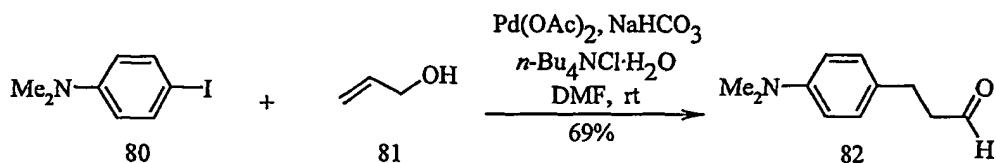
Step 2: To amide 78 (2.3 g, 13 mmol) in THF (25 mL) was added LiAlH₄ (970 mg, 25 mmol) portionwise over 5 minutes. The reaction mixture was heated to reflux for 1 hour, cooled in an ice/H₂O bath, carefully quenched with methanol, filtered through Celite, and the filtrate was concentrated under reduced pressure.

5 The residue was purified by flash chromatography (silica, 90:9.5:0.5 methylene chloride:methanol:NH₄OH) gave 3-(4-fluoro-2-methylphenyl)-1-propylamine 79 (580 mg, 22%), as the HCl salt: ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.05 (br s, 3H), 7.20-7.14 (m, 1H), 7.03-6.91 (m, 2H), 2.80 (dd, *J* = 8, 6 Hz, 2H), 2.63 (dd, *J* = 8, 8 Hz, 2H), 2.29 (s, 3H), 1.88-1.76 (m, 2H).

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Scheme 14

Preparation of 3-(4-Dimethylaminophenyl)propionaldehyde 82



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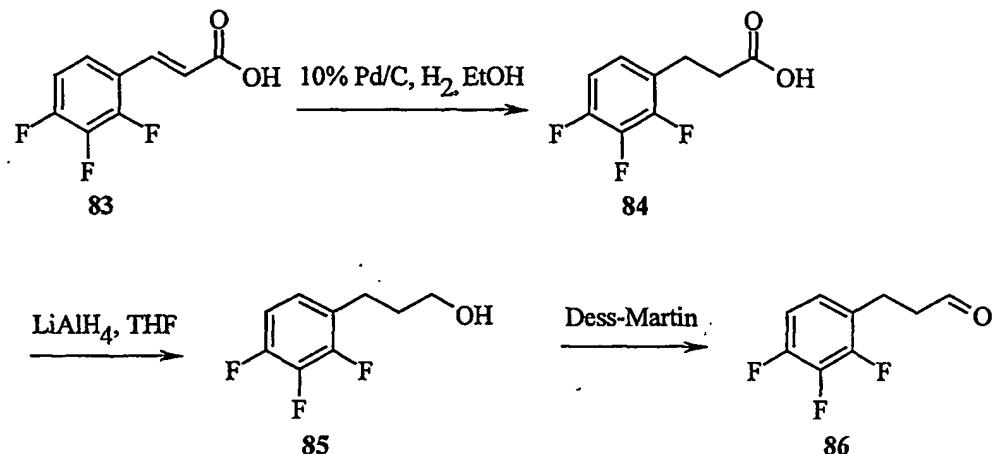
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Alcohol 81 (2.80 mL, 56.5 mmol), (4-iodophenyl)dimethylamine 80 (5.04 g, 20.4 mmol), sodium bicarbonate (4.30 g, 51.2 mmol), and tetrabutylammonium chloride hydrate (5.68 g, 20.4 mmol) were combined in DMF (25 mL). The reaction mixture was deoxygenated by passing a stream of argon through the solution for 15 minutes. Palladium(II) acetate (59 mg, 0.24 mmol) was added, and a stream of argon was again bubbled through the mixture for 10 minutes. After stirring under an argon atmosphere for 62 hours, the reaction mixture was partitioned between EtOAc (300 mL) and water (200 mL). The organic layer was separated, washed with water (3 × 200 mL) and saturated NaCl (200 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by chromatography (silica, 9:1 to 3:2 hexanes:EtOAc) gave 3-(4-dimethylaminophenyl)propionaldehyde 82 (910 mg, 25%): ¹H NMR (300 MHz, CDCl₃): δ 9.82 (s, 1H), 7.08 (d, *J* = 8 Hz, 2H), 6.70 (d, *J* = 8 Hz, 2H), 2.91 (s, 6H), 2.90-2.85 (m, 2H), 2.73 (dd, *J* = 8, 7 Hz, 2H).

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Scheme 15

Preparation of 3-(2,3,4-Trifluorophenyl)propionaldehyde **86**



Step 1: Hydrogenation of cinnamic acid **83** (5.0 g, 25 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, except 10% Pd/C was used, gave acid **84** (5.0 g, 99%): ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.25-7.14 (m, 2H), 2.85 (dd, *J* = 8, 7 Hz, 2H), 2.54 (dd, *J* = 8, 7 Hz, 2H).

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Step 2: Reduction of acid **84** (5.0 g, 24 mmol) with LiAlH₄ (930 mg, 24 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol **85** (4.6 g, 100%): ¹H NMR (300 MHz, DMSO-*d*₆): δ 7.23-

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7.11 (m, 2H), 4.45 (t, *J* = 5 Hz, 1H), 3.42 (dd, *J* = 6, 6 Hz, 2H), 2.66 (dd, *J* = 8, 8 Hz, 2H), 1.70-1.63 (m, 2H).

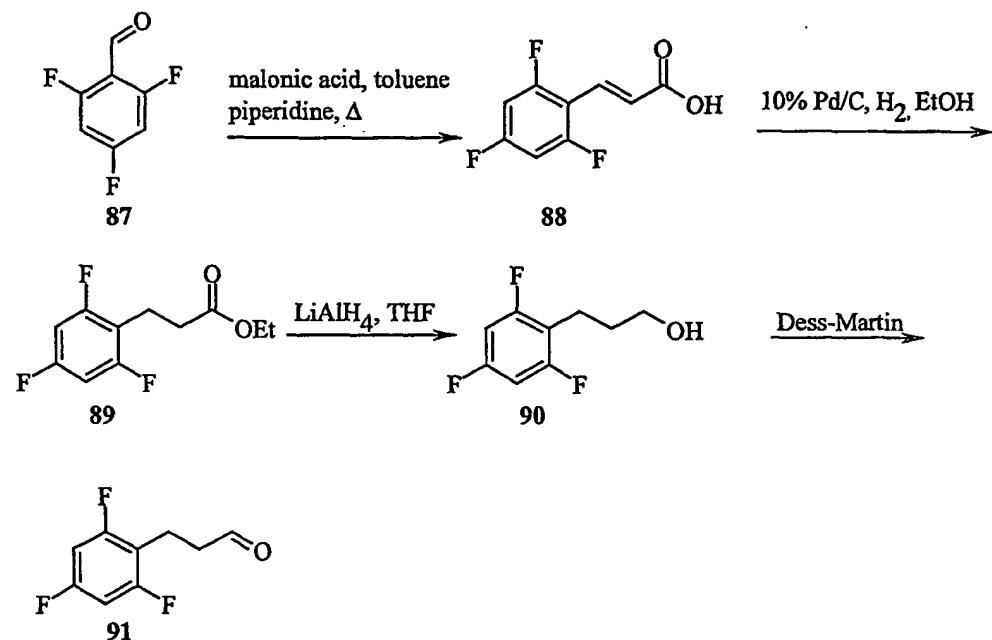
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Step 3: A mixture of alcohol **85** (1.0 g, 5.3 mmol), Dess-Martin periodane (4.5 g, 11.0 mmol), and water (0.1 mL) in CH₂Cl₂ (50 mL) was stirred for 4 hours. The reaction mixture was diluted with CH₂Cl₂ (40 mL), filtered through Celite, and the resulting filtrate concentrated under reduced pressure. Purification by chromatography (silica, 9:1 hexanes:EtOAc) gave 3-(2,3,4-trifluorophenyl)-propionaldehyde **86** (280 mg, 28%) as an oil: ¹H NMR (300 MHz, DMSO-*d*₆): δ 9.71 (s, 1H), 7.34-7.17 (m, 2H), 2.89-2.81 (m, 4H).

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Scheme 16

Preparation of 3-(2,4,6-Trifluorophenyl)propionaldehyde **91**



Step 1: Reaction of 2,4,6-trifluorobenzaldehyde (4.7 g, 29 mmol), malonic acid (3.4 g, 32 mmol), piperidine (0.14 mL, 1.4 mmol), and toluene (75 mL), following the procedure described in the General Procedure, Scheme 8, Step 1, gave cinnamic acid **88** (2.2 g, 37%): ¹H NMR (300 MHz, CDCl₃): δ 7.80 (dd, *J* = 16 Hz, 1H), 6.79-6.65 (m, 3H), 6.97 (dd, *J* = 8, 8 Hz, 1H).

Step 2: Hydrogenation of cinnamic acid **88** (2.2 g, 11 mmol), following the procedure described in the General Procedure, Scheme 8, Step 2, except 10% Pd/C was used, gave ethyl ester **89** (2.2 g, 88%): ¹H NMR (300 MHz, CDCl₃): δ 6.72-6.62 (m, 2H), 3.73 (q, *J* = 14, 7 Hz, 2H), 3.02-2.94 (m, 2H), 2.64 (dd, *J* = 7, 7 Hz, 2H), 1.25 (t, *J* = 7 Hz, 3H).

Step 3: Reduction of ester **89** (2.2 g, 11 mmol) with LiAlH₄ (410 mg, 11 mmol), following the procedure described in the General Procedure, Scheme 8, Step 3, gave alcohol **90** (470 mg, 26%): ¹H NMR (500 MHz, DMSO-*d*₆): δ 7.19-7.07 (m, 2H), 4.47 (t, *J* = 5 Hz, 1H), 6.83 (dd, *J* = 8, 6 Hz, 2H), 2.61 (dd, *J* = 8, 8 Hz, 2H), 1.66-1.61 (m, 2H).

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Step 4: A mixture of alcohol 90 (470 mg, 2.50 mmol), Dess-Martin periodane (2.1 g, 4.90 mmol), and water (0.04 mL) in CH₂Cl₂ (25 mL) was stirred for 3 hours. The reaction mixture was filtered through Celite and the resulting filtrate concentrated under reduced pressure. Purification by chromatography (silica, 5:1 hexanes:EtOAc) gave 3-(2,4,6-trifluorophenyl)-propionaldehyde 91 (360 mg, 76%) as an oil: ¹H NMR (300 MHz, DMSO-d₆): δ 9.67 (s, 1H), 7.22-7.13 (m, 2H), 2.82-2.80 (m, 2H), 2.75-2.72 (m, 2H).

Electrophysiological Assays at NMDA Receptor Subunits

Preparation of RNA. cDNA clones encoding the NR1A, NR2A, NR2B, and NR2C rat NMDA receptor subtypes were used (see, Moriyoshi, *supra.*, 1991; Kutsuwada et al., *supra.*, 1992; Monyer et al., *supra.*, 1992; Ikeda et al., *FEBS Lett.*, 1992;313:34-38; Ishii et al., *J. Biol. Chem.*, 1993;268:2836-2843 for details of these clones or their mouse homologs). The clones were transformed into appropriate host bacteria and plasmid preparations were made with conventional DNA purification techniques. A sample of each clone linearized by restriction enzyme digestion of cRNA was synthesized with T3 RNA polymerase. The cRNA was diluted to 400 ng/μL and stored in 1-μL aliquots at -80°C until injection.

The Xenopus oocyte expression system. Mature female *Xenopus laevis* were anaesthetized (20-40 minutes) using 0.15% 3-aminobenzoic acid ethyl ester (MS-222), and 2 to 4 ovarian lobes were surgically removed. Oocytes at developmental stages IV-VI (Dumont J.N., *J. Morphol.*, 1972;136:153-180) were dissected from the ovary still surrounded by enveloping ovarian tissues. Follicle-enclosed oocytes were microinjected with 1:1 mixtures of NR1A:NR2A, 2B or 2C; injecting 1 to 10 ng of RNA encoding each receptor subunit. NR1A encoding RNA was injected alone at ~20 ng. Oocytes were stored in Barth's medium containing (in mM): NaCl, 88; KC1, 1; CaCl₂, 0.41; Ca (NO₃)₂, 0.33; MgSO₄, 0.82; NaHCO₃, 2.4; HEPES 5; pH 7.4, with 0.11 mg/mL gentamicin sulphate. While oocytes were still surrounded by enveloping ovarian tissues, the Barth's medium was supplemented with 0.1% bovine serum. Oocytes were defolliculated 1 to 2 days following injections by treatment with collagenase (0.5 mg/mL Sigma

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Type I for 0.5-1 hr) – (Miledi and Woodward, *J. Physiol. (Lond.)* 1989;416:601-621) and subsequently stored in serum-free medium.

5 Electrical recordings were made using a conventional two-electrode voltage clamp (Dagan TEV-200) over periods ranging between 3 to 21 days following injection (Woodward et al., *Mol. Pharmacol.*, 1992;41:89-103). Oocytes were placed in a 0.1-mL recording chamber continuously perfused (5 mL-15 mL min⁻¹) with frog Ringer's solution containing (in mM): NaCl, 115; KCl, 2; BaCl₂, 1.8; HEPES, 5; and pH 7.4. Drugs were applied by bath perfusion. Using oocytes expressing different subunit combinations of NMDA 10 receptor, NMDA currents were activated by co-application of glutamate (100 μM) and glycine (1 -100 μM). Inhibitory potency of the novel antagonists was assessed on responses elicited by fixed concentrations of glutamate and glycine, by measuring reductions in current induced by progressively increasing concentrations of antagonist.

15 Concentration-inhibition curves were fit with Equation 1.

$$\frac{I}{I_{\text{control}}} = 1/(1 + ([\text{antagonist}]/10^{-\text{pIC}_{50}})^n)$$

Eq. 1

In which I_{control} is the current evoked by agonists alone, $\text{pIC}_{50} = -\log \text{IC}_{50}$, IC_{50} is the concentration of antagonist that produced half maximal inhibition, and n is the slope factor (De Lean et al., *Am. J. Physiol.*, 1978;235:E97-102). For incomplete curves, analysis by fitting was unreliable and IC_{50} values were calculated by simple regression over linear portions of the curves (Origin: Microcal Software).

The electrophysiological assay results are set forth in Table 1.

6-OHDA Lesioned Rat Assay:

25 6-Hydroxydopamine-lesioned rats were used (see Ungerstedt U., Arbuthnott G.W., Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. *Brain Res.*, 1971;24(3):485-93). Adult male Sprague-Dawley rats were anesthetized with chloral hydrate and unilateral lesions of the nigrostriatal dopamine system were

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accomplished by infusion of 8 µg of 6-hydroxydopamine HBr (6-OHDA) into the right medial forebrain bundle. Rats were pretreated 30 minutes before surgery with desipramine HC1 25 mg/kg intraperitoneally (IP) to protect noradrenergic neurons, and pargyline 25 mg/kg IP to potentiate the effects of 6-OHDA. A 5 minimum of 3 weeks after surgery, the rotational behavior induced by apomorphine HCL 50 µg/kg subcutaneously (SC) was assessed. Only rats demonstrating more than 100 contraversive turns/hour to apomorphine were used for the present experiments.

Rotational behavior was measured using an automatic rotometer system 10 (Rotorat Rotational Activity System, MED Associates, Georgia, Vermont). Anti-parkinsonian activity was assessed as the ability of the compound to potentiate the contraversive rotation induced by L-DOPA methyl ester, 10 mg/kg SC, over a 6-hour period. Experiments were conducted using a crossover paradigm where each rat received either a vehicle plus L-DOPA, or the test compound plus 15 L-DOPA, in randomized order. Rats were tested at 7-day intervals. In experiments in which the compound was tested orally, rats were food deprived for 16 hours. Statistical analysis between treatment groups were performed using a paired t-test. The results were reported in Table 1 as the minimum effective dose (MED) of compound (mg/kg) required to produce a statistically-significant increase in total 20 contraversive rotations compared to rats receiving L-DOPA only.

[³H]Ifenprodil Binding Assay Protocol:

MATERIALS and METHODS

All buffers and reagents used in assay incubations or to dissolve drugs 25 were prepared using water purified through a Milli-Q reverse osmosis system (Millipore Corp, Bedford, Massachusetts) and treated with UV emissions. Prior to use in the assays, buffers were further filtered through a sterile Corning filtration unit (Corning Glass Works, Corning, New York) containing a 0.2-micron filter. Buffer used to rinse the membranes on the assay filters was prepared with purified water, but was not refiltered and was stored no longer than 5 days. Stock solutions 30 of the drugs (usually 10 mM) were dissolved in 20 mM HEPES-KOH buffer

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pH 7.4 (assay buffer) with the addition of 1 to 5 μ L of glacial AcOH, if needed to keep them in solution. For eliprodil the stock solution was buffered with the addition of 10% DMSO. All subsequent dilutions from stock were made in buffer.

Membrane Preparation

5 An extensively washed buffy coat membrane fraction was prepared from frozen adult rat forebrains (Zivic-Miller Laboratories, Inc., Zelienople, Pennsylvania) as described previously (Coughenour L.L., Cordon, J.J., J. *Pharmacol. Exp. Ther.*, 1997;280:584-592) and stored at -80°C. On the day of the assay, pellets were resuspended in 35 mL of assay buffer at pH 7.4 using a
10 Polytron setting 6. After incubation at 37°C for 30 minutes in a shaking water bath, the homogenate was centrifuged 40,000 \times g for 10 minutes at 4°C. The pellets were resuspended in fresh buffer and centrifuged 3 more times before final suspension for use in the assay.

Binding Studies

15 **[3 H]Ifenprodil Binding.** Triplicate incubations were carried out in a volume of 0.5 mL in 1.3 mL polypropylene tubes (Marsh Biomedical Products Inc., Rochester, New York) for 2 hours at room temperature. Incubations contained test agents, membranes (100-200 μ g protein) and 4 nM [3 H]-ifenprodil in 20 mM HEPES-KOH buffer, pH 7.4 (assay buffer). Assays were started by
20 addition of the membranes. Bound radioligand was separated by filtration under reduced pressure using a Tomtec Mach II, 96-well cell harvester (Tomtec Inc., Orange, Colorado). Filtration was through Whatman GF/B glass fiber filters (Whatman Ltd, Maidstone, England), which had been soaked for at least 15 minutes in 0.3% polyethylenimine and allowed to air dry. The filters were
25 rinsed with 3 mL of ice cold assay buffer within 6 seconds. Air was allowed to pass through the filters for an additional 10 seconds to remove residual moisture. The filter mat was supported on a cold (-20°C) teflon support, and filters from individual wells were separated and placed in Mini Poly-Q vials (Beckman Instruments Inc., Fullerton, California) and filled with 4 mL of scintillation
30 cocktail (Beckman Ready Protein $^+$). Radioactivity retained on the filter was determined by liquid scintillation spectrophotometry. Nonspecific binding was

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defined as the binding in the presence of 1 mM ifenprodil. Specific binding was 90%.

[³H]-TCP binding. Binding assays were carried out essentially as described for [³H]ifenprodil binding. Incubations contained test agents, 100 to 5 200 µg protein, 2 nM [³H]-TCP, and 10 µM glutamate, glycine and spermidine. Incubations were for 10 minutes to allow assays to be carried out under nonequilibrium conditions for the detection of binding selective to NMDA receptors of the NR2B subtype. Specific binding was defined as the binding displaced by 100 µM (+)MK-801 and was 90% of the total binding.

10 Data analysis. Binding curves were statistically analyzed for a best one or two site competition fit using GraphPad Prism software (GraphPad Software Inc., San Diego, California). The normalized data was fit by nonweighted nonlinear regression to either

$$y = \text{Bottom} + \frac{(\text{Top-Bottom})}{1 + 10^{x-\text{LogEC50}}}$$

15 or

$$y = \text{Bottom} + (\text{Top-Bottom}) \frac{\text{Fraction -1}}{1 + 10^{x-\text{LogEC50}_1}} + \frac{1-\text{Fraction -1}}{1 + 10^{x-\text{LogEC50}_2}}$$

Control data was entered as 100%, and no parameters were constrained. Inhibition curves were compared by ANOVA with post test comparisons of the logIC₅₀ using Dunnett's multiple comparisons post test or Student's nonpaired, 20 two-tailed t-test (GraphPad InStat software).

25 Materials. TCP, [piperidyl-3,4-³H(N)]- (specific activity, 45-50 Ci/mmol) and ifenprodil, [phenyl-³H]- (specific activity, 66.2 Ci/mmol) were purchased from Dupont NEN Research Products (Boston, Massachusetts). Ifenprodil tartrate, trifluperidol hydrochloride, and GBR-12909 dihydrochloride were purchased from Research Biochemicals International (Natick, Massachusetts). Spermidine trihydrochloride was purchased from United States Biochemical Corp (Cleveland, Ohio). HEPES, glutamate, and glycine were purchased from Sigma Chemical Co, (St. Louis, Missouri). Haloperidol was obtained from McNeil Laboratories

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(Raritan, New Jersey) or Research Biochemicals International. Eliprodil was synthesized by Thomas Malone (Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan), and (+)MK-801 was synthesized by Leonard Lescosky (Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan).

5

TABLE 1

Example	NR1A/NR2B	[³ H]Ifenprodil	6-OHDA
	Oocyte IC ₅₀ (μM)	IC ₅₀ (μM)	MED (mg/kg)
1	0.03	0.004	30 (active)
2	0.10	0.040	10.0 (active)
3	0.10	0.034	10.0 (active)
4a	0.02	0.007	10.0 (inactive)
5a	0.02	0.004	
5b		0.021	
6		0.009	
7	0.09	0.037	
8	0.02		
9	0.06	0.015	
10	0.11	0.049	
11a	55.00	>1	
11b	10	>1	
12	70	22.5	
13a	0.08	0.038	
13b	0.02	0.005	
14		0.128	

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TABLE 1 (cont'd)

Example	NR1A/NR2B	[³ H]Ifenprodil	6-OHDA
	Oocyte IC ₅₀ (μM)	IC ₅₀ (μM)	MED (mg/kg)
15	0.46	0.092	
16	2.50	1.730	
17		0.010	10 (active)
18	0.065	0.009	10 (active)
19		0.185	
20		0.025	30 (active)
21		0.016	10 (active)
22		0.053	10 (active)
23		0.038	10 (active)
24b		0.014	
25		0.079	10 (active)
26		0.188	
27		0.132	
28		0.184	
29		0.018	
30		0.219	
31		0.465	
32		0.158	
33		>1 μM	
34		0.152	
35		0.170	
36b		>1 μM	

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TABLE 1 (cont'd)

Example	NR1A/NR2B	[³ H]Ifenprodil	6-OHDA
	Oocyte IC ₅₀ (μM)	IC ₅₀ (μM)	MED (mg/kg)
37b		0.032	
38b		0.007	
39b		0.037	
40b		0.029	
41b		0.068	
42b		0.980	
43b		0.056	
44b		0.007	
45b		0.007	
46b		0.009	
47b		0.015	
48b		0.020	
49b		0.022	
50b		0.351	
51b		0.550	
52b		0.003	
53		0.002	
54		0.034	
55		0.005	
56		0.071	
57		0.006	
58		0.357	

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TABLE 1 (cont'd)

Example	NR1A/NR2B	[³ H]Ifenprodil	6-OHDA
	Oocyte IC ₅₀ (μ M)	IC ₅₀ (μ M)	MED (mg/kg)
59		0.316	
60		>1 μ M	
61b		0.012	
62		0.017	
63		0.002	
64		0.045	
65		0.067	

While the forms of the invention exemplified herein such as, for example, the named species of Formulas I-III and the recitation of treatment of Parkinson's constitute presently preferred embodiments, many others are possible. It is not intended that said recited species of Formulas I-III and preferred methods of use should, in any manner, limit or restrict the invention from the full scope claimed herein. It is not intended herein to name all of the possible equivalent forms or ramifications of the invention. It is understood that the terms used herein are merely descriptive, rather than limiting. For example, the term "Parkinson's disease" is merely descriptive, and not limiting, of the term "neurodegenerative disease."

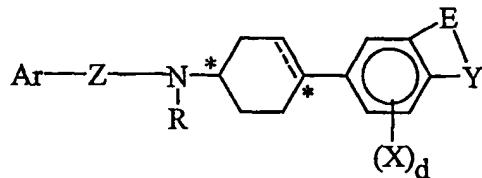
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CLAIMS

What is claimed is:

1. Bicycle-substituted cyclohexyl amines of Formula 1 and their pharmaceutically acceptable salts thereof

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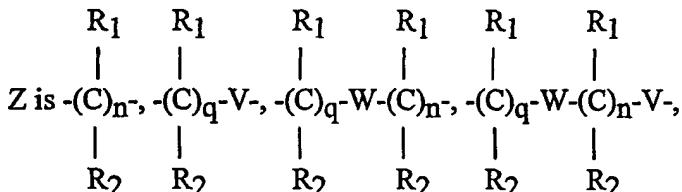
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wherein:

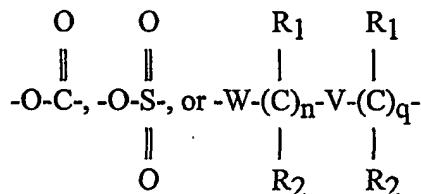
Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to 3 times or unsubstituted heteroaryl, which heteroaryl is from 5 to 14 atoms having from 1 to 2 heteroatoms selected from N, O, and S wherein the substituents are selected from the groups F, Cl, Br, I, OH, NH₂, SH, CN, NO₂, OCH₃, OC(O)CH₃, CF₃, OCH₂CH₂OH, NHC(O)CH₃, NHCH₃, or N(CH₃)₂;

10

15



20



25

wherein V is -(CH₂)_n-, -C-, -S(O)-, or -S(O)₂-,



W is -(CH₂)_n-, -C-, -S(O)-, -S(O)₂-, -O-, -S-, -C≡C-, or *entgegen* or *zusammen* -CH(R₁)=CH(R₂)-,

30

d is an integer from 0 to 2;

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- n is an integer from 1 to 6;
q is an integer from 0 to 6;
R₁ and R₂ are independently selected from the group consisting of
hydrogen, alkyl, OH, hydroxyalkyl, aminoalkyl, aralkyl, or
5 N(R₄)(R₅) wherein R₄ and R₅ are independently selected from
hydrogen, alkyl, aralkyl, heteroaryl, heteroaralkyl, aminoalkyl,
hydroxyalkyl, and thioalkyl;
R is hydrogen, alkyl, C(O)R₆, C(O)OR₆, C(O)NHR₆, -alkyl-C(O)NH₂,
aralkyl, (C₃-C₇ cycloalkyl)-alkyl, hydroxyalkyl, aminoalkyl,
10 amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenylalkyl, or
OH wherein R₆ is alkyl or aralkyl;
X is independently selected from hydrogen or an electron withdrawing
group;
-E-Y- is -CH=CH-N(H)-;
15 -(CH₂)₂-N(H)-,
-CH=N-N(H)-,
-C(O)-CH₂-N(H)-,
-CH₂-C(O)-N(H)-,
-CH₂-S(O)-N(H)-,
20 -CH₂-S(O)₂-N(H)-,
-CH=CH-CH(OH)-,
-(CH₂)₂-CH(OH)-,
-C(O)-CH₂-C(O)-,
-C(O)-NH-C(O)-,
25 -N=CH-N(H)-,
-N(H)-C(O)-N(H)-,
-O-C(O)-NH-,
-S-C(O)-NH-,
-O-N=CH(OH)-,
30 -S-N=CH(OH)-,
-N=N-N(H)-,
-CH=CH-CH=C(OH)-,

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-(CH₂)₃-CH(OH)-,
 -(CH₂)₂-S(O)-N(H)-,
 -(CH₂)₂-S(O)₂-N(H)-,
 -CH=CH-C(O)-N(H)-,
 5 -C(O)-NH-N=C(OH)-,
 -CH=N-NH-C(O),
 -CH=N(O)-N=C(OH)-,
 -N(H)-C(O)-N(H)-C(O)-,
 -N=CH-C(O)-NH-,
 10 -O-CH₂-C(O)-NH-,
 -S-CH₂-C(O)-NH-, or
 -N(H)-C(O)-C(O)-N(H)-,

---denotes a single or double bond; and

* denotes *cis* or *trans* or a mixture thereof.

15 2. A compound according to Claim 1 wherein:

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl CF₃, C(O)CH₃, and haloalkyl.

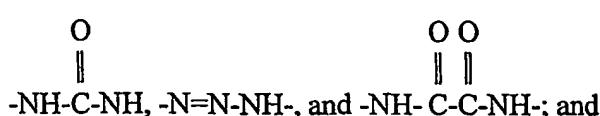
20 3. A compound of Claim 1 wherein:

Ar is unsubstituted or substituted phenyl;

X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF₃, C(O)CH₃, and haloalkyl;

25

-E-Y- is selected from -O-C(=O)-NH, -S-C(=O)-NH-, -CH=CH-NH-, -N=CH-NH-,



30

* denotes *trans*.

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4. A compound according to Claim 1 wherein:

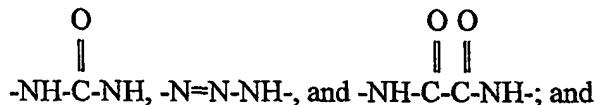
Ar is unsubstituted or substituted phenyl;

Z is a group whereby Ar and the nitrogen atom in Formula I are separated by from 2 to 4 atoms;

5 X is independently selected from hydrogen or an electron withdrawing group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF₃, C(O)CH₃, and haloalkyl;



10 -E-Y- is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-,



* denotes *trans*.

- 15 5. A compound according to Claim 1 wherein:

Ar is unsubstituted or substituted phenyl;



20 $\begin{array}{c} \text{OH} & \text{CH}_3\text{O} \\ | & | \quad || \\ -(\text{CH}_2\text{)}_m\text{-CH-H}_2\text{-, -O-C-C-, -S-(CH}_2\text{)}_m\text{-, -C}\equiv\text{C-CH}_2\text{, or} \\ -\text{C}\equiv\text{C-(CH}_2\text{)}_2\text{-} \end{array}$

wherein m is an integer 2 or 3;

25 R is hydrogen, H₂NC(O)alkyl, alkenylalkyl, methyl, heteroaralkyl, (C₃-C₇ cycloalkyl)alkyl, or C(O)CH₃;



30 $\begin{array}{c} \text{O} & & \text{O} \text{ O} \\ || & & || | \\ \text{-NH-C-NH, -N=N-NH-, and -NH-C-C-NH-;} \end{array}$

X is hydrogen; and

* denotes *trans*.

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6. A compound according to Claim 1 selected from:
- 6-[*trans*-4-(3-Phenylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[2-(4-Fluorophenoxy)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 5 6-[*trans*-4-(2-Phenoxyethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*cis*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 10 6-[*trans*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-[*cis*-4-(2-Phenylsulfanylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-[4-(3-Phenylpropylamino)cyclohex-1-enyl]-3*H*-benzoxazol-2-one;
- 15 6-{*trans*-4-[2-(4-Fluorophenylsulfanyl)ethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[(*R*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[(*S*)-1-Methyl-3-phenylpropylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 20 6-{*trans*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*cis*-4-[(1*S*,2*S*)-2-Hydroxy-2-(4-methoxyphenyl)-1-methylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[(1*S*,2*R*)-2-Hydroxy-1-methyl-2-phenylethylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 25 6-[*cis*-4-(3-*p*-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-[*trans*-4-(3-*p*-Tolylpropylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-[*trans*-4-(2-Benzenesulfinylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 30 6-[*trans*-4-(2-Benzenesulfonylethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[Methyl(3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;

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- 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*cis*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 5 6-{*trans*-[4-(2-Methyl-3-phenylpropylamino)cyclohexyl]}-3*H*-benzoxazol-2-one
- 6-{*trans*-4-[Methyl(2-methyl-3-phenylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-[4-(3-Phenyl-prop-2-yanylarnino)cyclohexyl]}-3*H*-benzoxazol-2-one;
- 10 6-{*trans*-4-[Methyl(3-phenylprop-2-yanyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[2-(4-Fluorophenylsulfanylethyl)methylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 15 6-{*trans*-4-[3-(4-Trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[Methyl-3-(p-tolylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[Methyl(2-phenoxyethyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 20 6-{*trans*-4-[Methyl-3-(4-trifluoromethylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(2,4-Difluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 25 6-(*trans*-4-{[3-(2,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(4-Isopropylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(4-Isobutylphenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 30 6-(*trans*-4-{[Ethyl-[3-(4-fluorophenyl)propyl]amino]cyclohexyl}-3*H*-benzoxazol-2-one;

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- 6-(*trans*-4-{Ethyl-[3-(4-trifluoromethylphenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{Ethyl-[(R)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 5 6-(*trans*-4-{Ethyl-[(S)-1-methyl-3-phenylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[[3-(4-Fluorophenyl)propyl]-2-hydroxyethyl]amino}-cyclohexyl}-3*H*-benzoxazol-2-one;
- 10 6-(*trans*-4-{Cyclopropylmethyl-[3-(4-fluorophenyl)propyl]amino}-cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]furan-3-cylmethylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{Allyl-[3-(4-Fluorophenyl)propyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 15 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]isobutylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{(2-Aminoethyl)-[3-(4-fluorophenyl)propyl]amino}-cyclohexyl)-3*H*-benzoxazol-2-one;
- 20 2-{[3-(4-Fluorophenyl)propyl]-[4-(2-oxo-2,3-dihydro-benzoxazol-6-yl)-cyclohexyl]amino}acetamide;
- (S)-6-{*trans*-4-[1-(4-Fluorophenylsulfanyl)pentan-2-ylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- (S)-6-{*trans*-4-[Ethyl(1-(4-fluorophenylsulfanyl)pentan-2-yl)amino]-cyclohexyl}-3*H*-benzoxazol-2-one;
- 25 6-[*trans*-4-(3-Phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-[*trans*-4-(Methyl-3-phenylbutylamino)cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(4-Chlorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 30 6-(*trans*-4-{[3-(4-Chlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(2,4-Dichlorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;

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- 6-(*trans*-4-[3-(3,5-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(3,5-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 5 6-(*trans*-4-[3-(3,4-Difluorophenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(3,4-Difluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 10 6-(*trans*-4-{[3-(2,3,4-Trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(4-{[3-(*trans*-4-Dimethylaminophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(2,4,6-Trifluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 15 6-(*trans*-4-[3-(2,4-Dimethylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-{4-[Methyl(2,4-dimethylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(2-Chloro-4-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 20 6-{*trans*-4-[3-(2-Chloro-4-fluorophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(4-Chloro-2-fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 25 6-(*trans*-4-{[3-(4-Chloro-2-fluorophenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-[3-(4-Fluoro-2-methylphenyl)propylamino]cyclohexyl)-3*H*-benzoxazol-2-one;
- 30 6-(*trans*-{4-[Methyl(4-fluoro-2-methylphenylpropyl)amino]cyclohexyl})-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(3-Fluoro-2-methylphenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;

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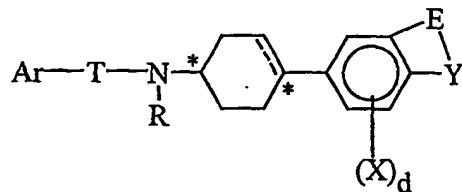
- 6-(*trans*-4-{[3-(3-Fluoro-2-methylphenyl)propyl]methylamino}-cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(2-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 5 6-(*trans*-4-{[3-(2-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-(3-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-(*trans*-4-{[3-(3-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 10 6-{*trans*-4-[3-Cyclohexylpropyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[3-Cyclohexylpropyl]methylamino}cyclohexyl)-3*H*-benzoxazol-2-one;
- 15 6-{*trans*-4-[4-(3-Thiophen-3-yl)propylamino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 6-[*trans*-4-{[3-(3-Thiophen-3-yl)propyl]methylamino}cyclohexyl]-3*H*-benzoxazol-2-one;
- 6-{*trans*-4-[Methyl(3-thiazol-2-ylpropyl)amino]cyclohexyl}-3*H*-benzoxazol-2-one;
- 20 6-(*trans*-4-{Methyl-[2-(methylphenylamino)ethyl]amino}cyclohexyl)-3*H*-benzoxazol-2-one;
- N-(2-{Methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-ethyl)benzamide;
- 25 N-{2-[4-(2-Oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexylamino]ethyl}-benzamide;
- 6-{*trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-3*H*-benzthiazol-2-one;
- 3-(4-Fluorophenyl)-N-methyl-N-[*trans*-4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]propionamide;
- 30 6-(*trans*-4-{[3-(4-Fluorophenyl)propyl]methylamino}cyclohexyl)-3*H*-benzthiazol-2-one;

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- 5-*{trans*-4-[3-(4-Fluorophenyl)propylamino]cyclohexyl}-1,3-dihydrobenzoimidazol-2-one;
 5-*(trans*-4-[[3-(4-Fluorophenyl)propyl]methylamino]cyclohexyl)-1,3-dihydrobenzoimidazol-2-one;
 5 6-(4-[[3-(4-Fluorophenyl)propyl]methyl-amino]cyclohexyl)-5-methyl-3*H*-benzoxazol-2-one; and
 6-*(trans*-4-[[3-(4-Fluorophenyl)propyl]methylamino]cyclohexyl)-5-methoxy-3*H*-benzoxazol-2-one.

7. A compound of Formula II

10



II

or a pharmaceutically acceptable salt thereof wherein:

Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to

3 times or unsubstituted heteroaryl, which heteroaryl is from 5 to 14 atoms having from 1 to 2 heteroatoms selected from N, O, and S

15

wherein the substituents are selected from the groups F, Cl, Br, I, OH, NH₂, SH, CN, NO₂, OCH₃, OC(O)CH₃, CF₃, OCH₂CH₂OH, NHC(O)CH₃, NHCH₃, or N(CH₃)₂;

-E-Y- is selected from the group consisting of -CH=CH-N(H)-,

-(CH₂)₂-N(H)-,

20

-CH=N-N(H)-,

-C(O)-CH₂-N(H)-,

-CH₂-C(O)-N(H)-,

-CH₂-S(O)-N(H)-,

-CH₂-S(O)₂-N(H)-,

25

-CH=CH-CH(OH)-,

-(CH₂)₂-CH(OH)-,

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- C(O)-CH₂-C(O)-,
- C(O)-NH-C(O)-,
- N=CH-N(H)-,
- N(H)-C(O)-N(H)-,
- 5 -O-C(O)-NH-,
- S-C(O)-NH-,
- O-N=CH(OH)-,
- S-N=CH(OH)-,
- N=N-N(H)-,
- 10 -CH=CH-CH=C(OH)-,
- (CH₂)₃-CH(OH)-,
- (CH₂)₂-S(O)-N(H)-,
- (CH₂)₂-S(O)₂-N(H)-,
- CH=CH-C(O)-N(H)-,
- 15 -C(O)-NH-N=C(OH)-,
- CH=N-NH-C(O),
- CH=N(O)-N=C(OH)-,
- N(H)-C(O)-N(H)-C(O)-,
- N=CH-C(O)-NH-,
- 20 -O-CH₂-C(O)-NH-,
- S-CH₂-C(O)-NH-, or
- N(H)-C(O)-C(O)-N(H)-,
- 25 T is (A)₀₋₁-N-(U)₀₋₁-(C)_t- or (A)₀₋₁-N-(C)_t-(U)₀₋₁-,

$$\begin{array}{c} R_3 & & R_1 & & R_3 & R_1 \\ | & & | & & | & | \\ & & & & & \\ & & R_2 & & & R_2 \end{array}$$
- 30 wherein U is -CH₂-, -C-, -S(O)-, or -S(O)₂-,

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A is -CH₂- , -C-, -S(O)-, or -S(O)₂-,

t is an integer from 1 to 3,

5 R₁ and R₂ are independently selected from hydrogen, alkyl, OH,

hydroxyalkyl, aminoalkyl, thioalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, guanidinyl, (aminocarbonyl)alkyl-, carboxyalkyl-, (methylthio)-alkyl-, or N(R₄)(R₅) wherein R₄ and R₅ are

independently selected from hydrogen, alkyl, aralkyl, heteroaryl,

10 heteroaralkyl, ureidoalkyl, aminoalkyl, hydroxyalkyl, or thioalkyl,

R₃ is hydrogen, alkyl, OH, or aralkyl,

R is hydrogen, alkyl, C(O)R₆, C(O)OR₆, C(O)NHR₆, alkyl -CO₂NH₂,

aralkyl, hydroxyalkyl, (C₃-C₇ cycloalkyl) alkyl, aminoalkyl,

amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenyl-alkyl, or

15 OH wherein R₆ is alkyl or aralkyl;

X is independently selected from hydrogen or an electron withdrawing group;

— denotes a single or a double bond; and

* denotes *cis* or *trans* or a mixture thereof.

20 8. A compound according to Claim 7 wherein:

X is independently selected from hydrogen or an electron withdrawing

group selected from the group consisting of halogen, nitro, cyano,

aminoalkyl, CF₃, C(O)CH₃, and haloalkyl.

9. A compound according to Claim 7 wherein:

25 Ar is unsubstituted or substituted phenyl;

X is independently selected from hydrogen or an electron withdrawing

group selected from the group consisting of halogen, nitro, cyano,

aminoalkyl, CF₃, C(O)CH₃, and haloalkyl;

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-E-Y- is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-,



5 -NH-C-NH-, -N=N-NH-, and -NH-C-C-NH-; and

* denotes *trans*.

10. A compound according to Claim 7 wherein:

Ar is unsubstituted or substituted phenyl;

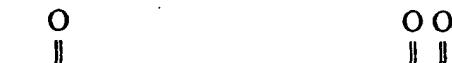
10 Ar and the nitrogen atom bearing R are separated by 3 or 4 atoms;

X is independently selected from hydrogen or an electron withdrawing

group selected from the group consisting of halogen, nitro, cyano, aminoalkyl, CF₃, C(O)CH₃, and haloalkyl.



15 -E-Y- is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-,



-NH-C-NH-, -N=N-NH-, and -NH-C-C-NH-; and

20 * denotes *trans*.

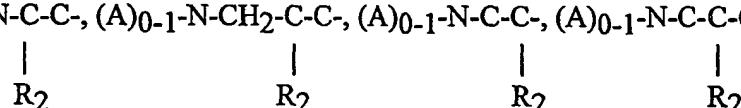
11. A compound according to Claim 7 wherein:

Ar is unsubstituted or substituted phenyl;

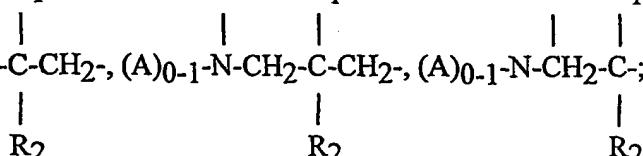
T is



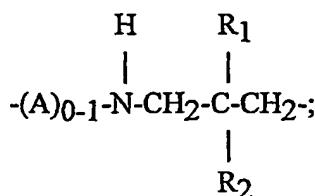
25 (A)₀₋₁-N-C-C-, (A)₀₋₁-N-CH₂-C-C-, (A)₀₋₁-N-C-C-, (A)₀₋₁-N-C-C-CH₂-,



30 -(A)₀₋₁-N-C-CH₂-, (A)₀₋₁-N-CH₂-C-CH₂-, (A)₀₋₁-N-CH₂-C-; or



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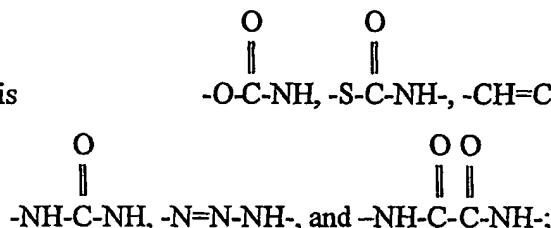


5

R is hydrogen, alkenylalkyl, H₂NC(O)alkyl, methyl, heteroaralkyl, (C₃-C₇ cycloalkyl)alkyl, or C(O)CH₃;

10

-E-Y-is -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-.



X is hydrogen; and

15

* denotes *trans*.

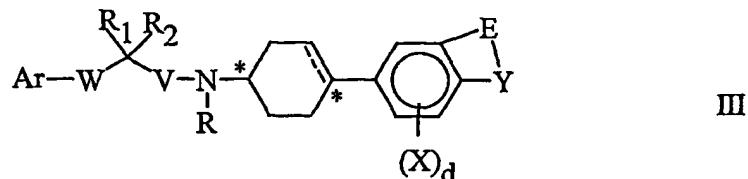
12. A compound according to Claim 7 selected from:

6-[*trans*-4-(2-Phenylaminoethylamino)cyclohexyl]-3*H*-benzoxazol-2-one;

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N-(2-{Methyl-[4-(2-oxo-2,3-dihydrobenzoxazol-6-yl)cyclohexyl]amino}-ethyl)benzamide.

13. A compound of Formula III



or a pharmaceutically acceptable salt thereof wherein:

Ar is substituted 1 to 3 times or unsubstituted aryl or substituted 1 to

25

3 times or unsubstituted heteroaryl, which heteroaryl is from 5 to 14 atoms having from 1 to 2 heteroatoms selected from N, O, and S wherein the substituents are selected from the groups F, Cl, Br, I, OH, NH₂, SH, CN, NO₂, OCH₃, OC(O)CH₃, CF₃, OCH₂CH₂OH, NHC(O)CH₃, NHCH₃, or N(CH₃)₂.

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- E-Y- is selected from the group consisting of -CH=CH-N(H)-,
-(CH₂)₂-N(H)-,
-CH=N-N(H)-,
-C(O)-CH₂-N(H)-,
5 -CH₂-C(O)-N(H)-,
-CH₂-S(O)-N(H)-,
-CH₂-S(O)₂-N(H)-,
-CH=CH-CH(OH)-,
-(CH₂)₂-CH(OH)-,
10 -C(O)-CH₂-C(O)-,
-C(O)-NH-C(O)-,
-N=CH-N(H)-,
-N(H)-C(O)-N(H)-,
-O-C(O)-NH-,
15 -S-C(O)-NH-,
-O-N=CH(OH)-,
-S-N=CH(OH)-,
-N=N-N(H)-,
-CH=CH-CH=C(OH)-,
20 -(CH₂)₃-CH(OH)-,
-(CH₂)₂-S(O)-N(H)-,
-(CH₂)₂-S(O)₂-N(H)-,
-CH=CH-C(O)-N(H)-,
-C(O)-NH-N=C(OH)-,
25 -CH=N-NH-C(O),
-CH=N(O)-N=C(OH)-,
-N(H)-C(O)-N(H)-C(O)-,
-N=CH-C(O)-NH-,
-O-CH₂-C(O)-NH-,
30 -S-CH₂-C(O)-NH-, or
-N(H)-C(O)-C(O)-N(H)-;

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V is $-(\text{CH}_2)_n-$, $-\text{C}-$, $-\text{S}(\text{O})-$, or $-\text{S}(\text{O})_2-$;



5 W is $-(\text{CH}_2)_n-$, $-\text{C}-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, $-\text{O}-$, $-\text{S}-$, $-\text{C}\equiv\text{C}-$, or *entgegen* or
zusammen $-\text{CH}(\text{R}_1)=\text{CH}(\text{R}_2)-$;

d is an integer from 0 to 2;

n is an integer from 1 to 6;

10 q is an integer from 0 to 6;

R_1 and R_2 are independently selected from the group consisting of

hydrogen, alkyl, OH, hydroxyalkyl, aminoalkyl, aralkyl, or
 N(R_4)(R_5) wherein R_4 and R_5 are independently selected from
 hydrogen, alkyl, aralkyl, heteroaryl, heteroaralkyl, aminoalkyl,
 hydroxyalkyl, and thioalkyl;

15 R is hydrogen, alkyl, $\text{C}(\text{O})\text{R}_6$, $\text{C}(\text{O})\text{OR}_6$, $\text{C}(\text{O})\text{NHR}_6$, -alkyl-C(O)NH₂,
 aralkyl, (C_3 - C_7 cycloalkyl)-alkyl, aminoalkyl,
 amino(hydroxy)alkyl, carboxyalkyl, heteroaralkyl, alkenylalkyl, or
 OH wherein R_6 is alkyl or aralkyl;

20 X is independently selected from hydrogen or an electron withdrawing
 group;

— denotes a single or a double bond; and

* denotes *cis* or *trans* or a mixture thereof.

14. A compound according to Claim 3 wherein:

25 Ar is unsubstituted or substituted phenyl;

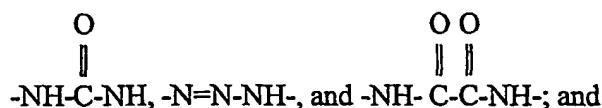
X is independently selected from hydrogen or an electron withdrawing

group selected from the group consisting of halogen, nitro, cyano,
 aminoalkyl, CF₃, C(O)CH₃, and haloalkyl;



30 ~E-Y- is selected from -O-C-NH-, -S-C-NH-, -CH=CH-NH-, -N=CH-NH-,

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* denotes *cis*.

- 5 15. A compound according to Claim 3 wherein:
 Ar is unsubstituted or substituted phenyl;
 X is independently selected from hydrogen or an electron withdrawing
 group selected from the group consisting of halogen, nitro, cyano,
 aminoalkyl, CF_3 , $\text{C}(\text{O})\text{CH}_3$, and haloalkyl;

10 $\begin{array}{c} \text{O} \quad \text{O} \\ || \quad || \\ -\text{E}-\text{Y}- \text{ is selected from } -\text{O}-\text{C}-\text{NH}, -\text{S}-\text{C}-\text{NH}-, -\text{CH}=\text{CH}-\text{NH}-, -\text{N}=\text{CH}-\text{NH}-, \end{array}$

15 $\begin{array}{c} \text{O} \quad \text{O} \\ || \quad || \\ -\text{NH}-\text{C}-\text{NH}, -\text{N}=\text{N}-\text{NH}-, \text{ and } -\text{NH}-\text{C}(=\text{O})-\text{C}(=\text{O})-\text{NH}-; \text{ and} \end{array}$

* denotes *trans*.

16. The compound of Claim 1, 7, or 3 wherein:

20 $\begin{array}{c} \text{O} \\ || \\ -\text{E}-\text{Y}- \text{ is } -\text{O}-\text{C}-\text{NH}. \end{array}$

17. The compound of Claim 1, 7, or 3 wherein:

$\begin{array}{c} \text{O} \\ || \\ -\text{E}-\text{Y}- \text{ is } -\text{NH}-\text{C}-\text{NH}. \end{array}$

- 25 18. The compound of Claim 1, 7, or 3 wherein:

$\begin{array}{c} \text{O} \\ || \\ -\text{E}-\text{Y}- \text{ is } -\text{S}-\text{C}-\text{NH}. \end{array}$

- 30 19. A pharmaceutical composition useful for treating disorders responsive to
 the selective blockade of N-methyl-D-aspartate receptor subtypes,
 optionally disorders as stroke, cerebral ischemia, trauma, hypoglycemia,
 neurodegenerative disorders, anxiety, depression, migraine headache,

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convulsions, aminoglycoside antibiotics-induced hearing loss, psychosis, glaucoma, CMV retinitis, opioid tolerance or withdrawal, chronic pain, or urinary incontinence the compositions comprising a pharmaceutically acceptable carrier or diluent and a therapeutically effective amount of at least one compound of Claim 1, Claim 7, or Claim 3.

- 5 20. A pharmaceutical composition according to Claim 19, wherein the neurodegenerative disorder is Parkinson's disease.
- 10 21. A pharmaceutical composition according to Claim 19, further comprising a dopamine agonist or precursor thereof in amount effective to treat Parkinson's disease.
- 15 22. A method for treating disorders responsive to the selective blockade of N-methyl-D-aspartate receptor subtypes in a mammal suffering thereof which comprises administering in unit dosage form at least one compound represented by Formula I of Claim 1 or Formula II of Claim 7 or Formula III of Claim 3.
- 20 23. A method according to Claim 22, wherein the disorder is Parkinson's disease.
24. A method according to Claim 22, further comprising administering in unit dosage form a compound any one of Formula I-III to a mammal suffering from Parkinson's disease.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/14763

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 7	C07D263/58	C07D277/68	C07D235/26	C07D413/12	C07D417/12

A61K31/423 A61K31/428 A61K31/4184 A61P25/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D C07C A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 982 026 A (F. HOFFMANN-LA ROCHE AG) 1 March 2000 (2000-03-01) the whole document -----	1-24
A	WO 99 48891 A (MERCK PATENT GMBH) 30 September 1999 (1999-09-30) the whole document -----	1,7,13, 19,22
A	DE 44 38 055 A (DR. KARL THOMAE GMBH) 2 May 1996 (1996-05-02) page 10, line 20, and page 15, line 6 -----	1,7,13

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

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- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority, claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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7 September 2001

13/09/2001

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Authorized officer

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INTERNATIONAL SEARCH REPORT

/ Information on patent family members

International Application No	
PCT/US 01/14763	

Patent document cited in search report	Publication date		Patent family member(s)		Publication date
EP 982026	A	01-03-2000	AU BR CN HR HU JP NO PL TR US	4453799 A 9903779 A 1248439 A 990256 A 9902737 A 2000109429 A 993948 A 334949 A 9902015 A 6184236 B	04-05-2000 19-09-2000 29-03-2000 30-04-2000 28-06-2000 18-04-2000 21-02-2000 28-02-2000 21-03-2000 06-02-2001
WO 9948891	A	30-09-1999	DE AU BR CN EP NO	19812331 A 3410599 A 9908902 A 1293673 T 1068202 A 20004668 A	23-09-1999 18-10-1999 28-11-2000 02-05-2001 17-01-2001 19-09-2000
DE 4438055	A	02-05-1996		NONE	